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Airway Obstruction and Mortality



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AIRWAY OBSTRUCTION AND MORTALITY

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ABSTRACT

Background and aims: Subjects with chronic obstructive pulmonary disease (COPD) have comorbidities and an increased mortality rate. However, long-term follow-up data on COPD and mortality appear incomplete. This study aimed to evaluate whether airway obstruction at baseline predicts acute myocardial infarction (MI) and coronary and all-cause mortality, and whether past pulmonary tuberculosis (TB) or a low vitamin D status confounds or modifies the association between obstruction and mortality during a 30-year follow-up.

Methods: A national health examination survey, the Mini-Finland Health Survey performed between 1978 and 1980, collected data among 8000 subjects in a sample representing the Finnish adult population. Studies I to IV consisted of 5576 to 6701 subjects who underwent spirometry at baseline and had all of the necessary information collected for each study. Baseline data were linked to follow-up data from various databases. Obstruction was defined either using a fixed ratio of the forced expiratory volume in 1 second per forced vital capacity (FEV_1/FVC) < 0.7 or FEV_1/FVC below the lower limit of normal (LLN) categorization, and staged for severity based on the Global Initiative for Chronic Obstructive Lung Disease classification (GOLD stages 1–4).

The cross-sectional baseline associations between obstruction and different characteristics were analyzed through logistic regression analysis, with the results expressed as adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs). In the cohort design, the Cox's proportional hazard model was used and the adjusted hazard ratios (HRs) with 95% CIs were estimated. Analyses were performed using the SAS System for Windows (SAS Institute, Inc., Cary, NC, version 9.1, 9.2, or 9.3) or IBM's SPSS Statistics (version 23 or 24).

Results: During follow-up, the GOLD stage had a strong significant association with all-cause mortality. Respectively, HRs (95% CIs) in GOLD stages 1–4 were 1.27 (1.06–1.51), 1.40 (1.21–1.63), 1.55 (1.22–1.97), and 2.85 (1.65–4.94) compared to those with $FEV_1/FVC \geq 0.7$. The risk for

cardiovascular mortality was consistently increased in GOLD stages 1–4 in age, sex, and smoking and in multivariate adjusted models, although no association emerged after excluding those with cardiovascular disease at baseline. GOLD stages 2–4 predicted all-cause mortality strongest in subjects aged 30 to 49 at baseline (study I).

In addition, obstruction predicted coronary mortality, but not MI among those without cardiovascular disease at baseline. Respectively, HRs (95% CIs) for coronary mortality and MI in subjects with obstruction were 1.40 (1.04–1.88) and 0.84 (0.54–1.31) when compared to those without. In the subgroup analysis, obstruction predicted MI and coronary death among women aged 30 to 49 at baseline (study II).

In addition, past pulmonary TB, determined either as a TB disease history or a scar indicated via chest x-ray, had an association with obstruction in a cross-sectional study. During follow-up, past TB and obstruction predicted all-cause mortality through an additive pattern (study III).

Finally, obstruction and vitamin D status predicted all-cause mortality independently of each other during follow-up. The association between a low vitamin D status and mortality was particularly pronounced among subjects with obstruction. Respectively, HRs (95% CIs) for subjects without and with obstruction in the highest tertiles of vitamin D status were 0.89 (0.81–0.98) and 0.57 (0.40–0.80) when compared to those with the lowest tertile (study IV).

Conclusions: Airway obstruction predicts all-cause mortality by decreasing lung function, and obstruction appears to increase mortality risk particularly in younger populations. Obstruction strongly determines coronary mortality, but not the risk of MI. Moreover, obstruction and past TB have an additive effect on all-cause mortality. Finally, a low vitamin D status may be particularly detrimental among subjects with obstruction.

Keywords: airway obstruction, mortality, epidemiological study, coronary mortality, myocardial infarction, pulmonary tuberculosis, serum 25-hydroxyvitamin D

YHTEENVETO

Esitiedot ja tutkimuksen tarkoitus: Keuhkohtaumatautiin liittyy muita pitkäaikaisia sairauksia ja ennenaikaisen kuoleman riski. Seurantatutkimuksia aiheista on melko niukasti ja tieto on vajavaista. Väitöskirjatutkimuksen tarkoituksena oli analysoida lähtötilanteen poikkileikkausasetelmassa mitatun keuhkoputkien ahtauman (obstruktion) yhteyttä eri tekijöihin ja arvioida kohorttiasetelmassa obstruktion ja näiden tekijöiden vaikutuksia kokonais- ja sepelvaltimotautikuolleisuuteen sekä akuutin sepelvaltimotautikohtauksen riskiin yli 30 vuoden seurannan aikana.

Metodit: Tutkimusaineistona oli Suomessa vuosina 1978–1980 toteutetun Mini-Suomi -väestötutkimuksen aineisto, johon yhdisteltiin rekisteriseurantatietoja. Tutkimukseen kutsuttu 8000 henkilön otos edusti suomalaista aikuisväestöä. Tämän väitöskirjatutkimuksen osatöiden analyyseissa olivat mukana ne 5576–6701 henkilöä, joilta löytyivät kussakin osatyössä tarvittut tiedot (sisältäen spirometrian). Obstruktio määriteltiin joko kiinteällä spirometrian raja-arvolla $FEV_1/FVC < 0.7$ tai iän, sukupuolen ja pituuden mukaan määritetyllä lower limit of normal -raja-arvolla (LLN) ja luokiteltiin vaikeusasteisiin 1–4 GOLD-luokituksen mukaisesti.

Obstruktion ja eri muuttujien poikkileikkausyhteyksiä analysoitiin logistisilla malleilla, jolloin tulokset ilmaistiin vakioituina vetosuhteina (odds ratio, OR) 95 %:n luottamusväleineen. Seurantatietoja analysoitiin Coxin mallilla (Cox's proportional hazards models), ja tulokset ilmaistiin riskitiheyssuhteina (hazard ratio, HR) 95 %:n luottamusväleineen. Tilastollisissa analyyseissa käytettiin joko SAS- (SAS System for Windows, versio 9.1, 9.2 tai 9.3, SAS Institute, Inc., Cary, NC) tai SPSS-järjestelmää (IBM SPSS statistics, versio 23 tai 24).

Tulokset: Mitä vaikeampi obstruktio perustutkimuksessa todettiin, sitä suurempaa kokonaiskuolleisuus oli seurannassa. Vastaavat HR-luvut (95 % luottamusväleillä) olivat GOLD-luokissa 1–4 1.27 (1.06–1.51), 1.40 (1.21–1.63), 1.55 (1.22–1.97) ja 2.85 (1.65–4.94), kun vertailuryhmänä olivat ne, joilla FEV_1/FVC oli ≥ 0.7 . Obstruktion ja kokonaiskuolleisuuden välillä oli

voimakkain yhteys nuorimmalla ikäryhmällä (30–49-vuotiailla). Sydän- ja verisuonisairauskuolleisuus oli lisääntynyt yhtä paljon kaikissa GOLD-luokissa. Yhteyttä ei enää todettu, kun mallista poistettiin ne henkilöt, joilla oli perustutkimuksessa todettu jokin muu sydän- tai verisuonisairaus kuin komplisoitumaton verenpainetauti (osatyö I).

Obstruktio ennusti seurantatutkimuksessa sepelvaltimotautikuolleisuutta, mutta ei akuuttia sydäninfarktia; vastaavat HR-luvut (95 % luottamusväleillä) sepelvaltimotautikuolleisuudelle ja akuutille sydäninfarktille olivat obstruktiivisilla 1.40 (1.04–1.88) ja 0.84 (0.54–1.31) verrattaessa niihin, joilla ei ollut obstruktiota. Osajoukottaisessa analyysissä obstruktio ennusti 30–49-vuotiailla naisilla akuuttia sydäninfarktia. Osatyön II analyyseistä oli suljettu pois ne henkilöt, joilla perustutkimuksessa oli todettu jokin muu sydän- tai verisuonisairaus kuin komplisoitumaton verenpainetauti (osatyö II).

Aikaisempi keuhkotuberkuloosi määriteltiin joko hoidettuna tautina tai keuhkojen röntgenkuvaan jääneenä tyypillisenä arpena. Aikaisemmalla keuhkotuberkuloosilla ja obstruktiolla oli kokonaiskuolleisuutta lisäävä additiivinen yhteisvaikutus. Vastaavat HR-luvut (95 % luottamusväleillä) olivat: niille joilla ei ollut aikaisempaa keuhkotuberkuloosia tai obstruktiota 1 (vertailuryhmä), niille joilla oli aikaisempi keuhkotuberkuloosi mutta ei obstruktiota 1.1 (1.0–1.2), niille joilla oli obstruktio mutta ei aikaisempaa keuhkotuberkuloosia 1.6 (1.3–2.0) ja niille joilla oli molemmat 1.8 (1.5–2.2) (osatyö III).

Alentunut D-vitamiinitaso ja obstruktio ennustivat toisistaan riippumatta kokonaiskuolleisuutta. Lisäksi todettiin tilastollisesti merkitsevä yhdysvaikutus ($p = 0,007$): matala D-vitamiinitaso oli voimakkaammin yhteydessä obstruktiivisten kuin muiden henkilöiden kuolleisuuteen. Vastaavat HR-luvut (95 % luottamusväleillä) olivat niillä, joilla ei ollut ja oli obstruktio korkeimmassa D-vitamiinitertiilissä 0.89 (0.81–0.98) ja 0.57 (0.40–0.80) verrattuna matalimpaan tertiiliin (osatyö IV).

Yhteenveto: Kokonaiskuolleisuus lisääntyy, kun obstruktio vaikeutuu. Obstruktio saattaa olla erityisen haitallista nuoremmassa ikäluokissa. Obstruktio ennustaa sepelvaltimotautikuolleisuutta, mutta ei akuuttia sydäninfarktia. Obstruktiolla ja aikaisemmalla keuhkotuberkuloosilla on

kuolleisuutta lisäävä additiivinen yhteisvaikutus. Matala D-vitamiinitaso voi lisätä enemmän obstruktiivisten kuin muiden henkilöiden ennenaikaista kuolleisuutta.

Avainsanat: obstruktio ilmateissä, epidemiologia, kuolleisuus, sepelvaltimotautikuolleisuus, sydäninfarkti, keuhkotuberkuloosi, seerumin 25-hydroksivitamiini-D

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Mattila T, Vasankari T, Kanervisto M, Laitinen T, Impivaara O, Rissanen H, Knekt P, Jousilahti P, Saarelainen S, Puukka P, and Heliövaara M. Association between all-cause and cause-specific mortality and the GOLD stages 1–4: A 30-year follow-up among Finnish adults. *Respir Med.* 2015; 109: 1012–8
- II Mattila T, Vasankari T, Rissanen H, Knekt P, Puukka P, Heliövaara M. Airway obstruction and the risk of myocardial infarction and death from coronary heart disease: a national health examination survey with a 33-year follow-up period. *Eur J Epidemiol.* 2017 Jul 7. doi: 10.1007/s10654-017-0278-3. Epub ahead of a print.
- III Mattila T, Heliövaara M, Rissanen H, Knekt, Puukka P, and Vasankari T. Tuberculosis, airway obstruction and mortality in a Finnish population. *COPD.* 2017 Apr;14(2):143-149.
- IV Mattila T, Vasankari T, Rissanen H, Knekt P, Sares-Jäske L, Jääskeläinen T, Heliövaara M. Airway obstruction, vitamin D status and mortality in a 33-year follow-up study. (Submitted 2018)

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ABBREVIATIONS

25(OH)D	25-Hydroxyvitamin D
ABCD	Assessment of COPD symptoms and risk of exacerbations
BMI	Body mass index [weight (kg)/height ² (m ²)]
BOLD	Burden of Obstructive Lung Disease
BTPS	Body temperature and pressure, saturated with water vapour value
CCHS	Copenhagen City Heart Study
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
EKG	Electrocardiogram
FEV ₁	Forced expiratory volume in 1 second
FEV ₁ /FVC	Forced expiratory volume in 1 second per forced vital capacity
FVC	Forced vital capacity
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GOLD stage	Classification of airway obstruction according to GOLD (stages 1–4)
HDL	High-density lipoprotein
HR	Hazard ratio
HUNT Study	Nord-Trondelag Health Study
ICD	<i>International Classification of Diseases</i>
LDL	Low-density lipoprotein
LLN	Lower limit of normal categorization for obstruction
MI	Acute myocardial infarction
NHANES	National Health Examination Survey
NHIS	National Health Information Survey
NSAID	Non-steroidal anti-inflammatory drug
OLIN Study	Obstructive Lung Disease in Northern Sweden Study
OR	Odds ratio
PLATINO Study	Latin American Project for the Investigation of Obstructive Lung Disease Study
SAPALDIA	Swiss study on air pollution and lung disease in adults
SD	Standard deviation
TB	Pulmonary tuberculosis
WHO	The World Health Organization

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease causing non-reversible airway obstruction and leading to major morbidity and mortality worldwide. It's suspected that COPD will be the third leading cause of death globally by 2020; in Finland, about 1000 individuals die from COPD yearly. The prevalence of COPD stood at 10.1% in an international study, and 3.6% in one Finnish study; another study placed prevalence in Finland at 4.3% in men and 3.1% in women. COPD is primarily caused by smoking, and smoking cessation represents the most effective way to slow disease progression and decrease mortality [1-7].

Morbidity and mortality increase as COPD progresses and lung function decreases. Multiple factors, such as an increasing age, male sex, and a low body mass index (BMI), predict mortality in subjects with COPD. Additionally, many comorbidities—for instance, cardiovascular diseases, osteoporosis, cancer, and depression—have associations with COPD, decrease the quality of life, and increase mortality [1,5,8-21]. As COPD progresses, the number and severity of comorbidities often increase as well. The link between COPD and comorbidities continues have association with the poorly understood systemic inflammatory pathway [1,8,12-14,22,23].

Cardiovascular diseases are among the most important comorbidities in COPD, where smoking is one of the main risk factors in cardiovascular diseases. Cardiovascular diseases are a common cause of death in subjects with COPD. Worldwide one in three deaths is caused by cardiovascular diseases—over 40% of cardiovascular deaths being coronary deaths [1,5,9,11,15,24].

In addition to comorbidities, subjects with COPD suffer other diseases and conditions which have associations with common risk factors for COPD, particularly smoking. These other diseases include, for instance, chronic bronchitis, idiopathic pulmonary fibrosis, asthma, past pulmonary TB, and a low vitamin D status [1,25-30]. Since unique data were available about past TB and vitamin D status, this thesis focused on the associations between these factors and obstruction as well as their joint effects on mortality.

Annually, about 9 million active tuberculosis infections occur globally; tuberculosis represents a major health problem causing unnecessary deaths when untreated. While tuberculosis is currently rare in Finland, prevalence was higher when the Mini-Finland Health Survey data were collected (50–80 cases per 100 000 population), comparable to rates found in developing countries today [31-33].

The current prevalence of low vitamin D status reaches up to 30% in Europe and 0.6% in Finland with the current vitamin D fortification policy; during the Mini-Finland Health Survey, vitamin D deficiency among Finns appeared higher [28,34,35]. A low vitamin D status, tuberculosis, and COPD

have all associations with similar factors, such as ageing, smoking, a low socioeconomic status, and chronic diseases [1,2,22,28,32,33,36-47].

The material in this doctoral study stems from the Mini-Finland Health Survey, the first Finnish population-based health examination survey with 7217 participants (90% of those invited participated) representing the adult Finnish population. Data were collected through interviews, clinical measurements, and examinations during the baseline study carried out from 1978 through 1980, and subsequently followed-up using record linkage to various registers, such as the causes of death from Statistics Finland [48,49].

For this doctoral study, data were analyzed for 5576 to 6701 study subjects with all the necessary records for each study, including spirometry. Analysis focused on the cross-sectional baseline associations between obstruction and various factors, controlling for those associations, and evaluating whether obstruction at baseline predicted various endpoints (myocardial infarction (MI) and coronary, cardiovascular, and all-cause mortality) during the three-decade follow-up after the baseline survey [48,50,51].

2 REVIEW OF THE LITERATURE

Resources for the literature review were obtained through a PubMed search concentrating on publications from the last 10 years and which appeared in good-quality journals. A massive amount of scientific research on COPD, comorbidities, and mortality resulted; thus, this review focuses, on the one hand, on the highest-quality studies, and, on the other hand, studies which best correspond to the national health examination survey data we analyzed. However, almost all studies on the associations between COPD and cardiovascular mortality relying on a comparable study design to the Mini-Finland Health Survey were performed 10 to 20 years ago, and were, therefore, included. In addition, limited data exist on some specifics, such as the effect of a low vitamin D status on mortality in subjects with COPD, and, therefore, all available resources related to such topics were used.

2.1 WHAT IS CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)?

The first Finnish doctoral study on respiratory symptoms, chronic bronchitis, and pulmonary emphysema was published in 1965 in material where 82.3% of men and 13.9% women smoked, concluding that a chronic cough had an association with smoking with a prevalence of 25.3% in men and 5.7% in women. Respectively, the prevalence rates for chronic bronchitis and emphysema were 28.2% and 10.0% in men and 5.8 and 2.3% in women, and, a lower FEV₁ had an association with smoking in men [52].

According to current data, COPD is primarily caused by smoking. However, in developing countries in particular never-smokers have COPD which appears to result from poverty related to in utero, early childhood exposures and continuing exposure to polluted air, smoke, dust, and fumes, as well as past TB [1,5,53].

COPD is defined as a chronic, progressive airway obstruction and chronic inflammation, and worldwide represents the most common chronic respiratory disease causing major unnecessary morbidity and mortality. Four characteristics contribute to COPD with varying roles in different patients: chronic bronchitis, airway obstruction, emphysema, and comorbidities. Chronic bronchitis is defined as a productive cough continuing for at least three months period and repeating at least two years after another; airway obstruction is defined as a decreased expirium caused by obstruction and emphysema; and emphysema is a non-reversible dilatation in dilated terminal airways and destroyed alveolar walls. Comorbidities include extra-pulmonary diseases which have association with COPD, such as cardiovascular diseases, metabolic syndrome, osteoporosis, and depression [1,7,36].

2.2 DEFINITIONS FOR OBSTRUCTION

No single definition for obstruction exists in international scientific use. This dissertation study was performed between 2010 and 2018, using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the lower limit of normal (LLN) definitions for obstruction [1,54-58].

GOLD is a committee of international COPD experts who provide annual updated recommendations for clinical use regarding the assessment, diagnosis, and treatment of COPD. During this doctoral study, GOLD specified COPD using three different definitions. Between 2001 and 2011, obstruction was defined using a fixed cut-off limit ($FEV_1/FVC < 0.7$) with the degree of COPD classified further based on GOLD stages 1–4 (Figure 1). Between 2011 and 2016, COPD was classified in ABCD groups which included, in addition to GOLD stages 1–4, respiratory symptoms and the number of COPD annual exacerbations. In these, COPD treatment recommendations were outlined based on the GOLD staging or ABCD classification. From 2017, GOLD classified COPD separately according to the degree of obstruction in GOLD stages 1–4 ($FEV_1/FVC < 0.7$) and in ABCD groups according to the respiratory symptoms and the risk of annual COPD exacerbation. Treatment is currently recommended based on ABCD classification, while the diagnosis, prognosis, and other therapeutic approaches are based on GOLD stages 1–4 [1,54,55].

The fixed cut-off limit for obstruction ($FEV_1/FVC < 0.7$) might overestimate COPD in the elderly and underestimate it in subjects under 45 years [1,54,55,59,60]. Therefore, use of the LLN definition, which categorizes the limit of obstruction individually for each subject according to their age, sex, and height, is recommended [56,58,61].

	FEV₁, % of predicted	Level of obstruction
GOLD 1	≥ 80%	Mild
GOLD 2	50% to 80%	Moderate
GOLD 3	30% to 50%	Severe
GOLD 4	< 30%	Very severe

Figure 1 GOLD stages according to GOLD in those with $FEV_1/FVC < 0.7$ [1].

2.3 REFERENCE VALUES FOR OBSTRUCTION

No single reference value for obstruction exists in international scientific use. This study used the Swiss study on air pollution and lung disease in adults (SAPALDIA) and the Global Lung Function Initiative (GLI) reference values for obstruction [56,58,62]. The SAPALDIA values, published in 1996, were determined for Swiss adults aged 18 to 60 and can be extrapolated up to age 75 [56,62]. The GLI values, published in 2012, were determined from multi-ethnic spirometry records from 97 759 healthy non-smokers aged 3 to 95 based on the age, sex, and height of subjects. Furthermore, the GLI values were determined separately for four ethnic groups, while genetic variations in the spirometry results were found in the populations (body composition and the size of the thoracic cavity). Caucasians were drawn from a wide variety of geographical regions, although no Finns were included. The classification for the degree of obstruction according to GLI was published in 2014. The GLI reference values are currently recommended for international use [58,63].

In Finnish clinical use, the 1982 reference values published by Viljanen et al. were determined from a selected occupational cohort of 553 subjects aged 18 to 65. Consequently, these values are not appropriate for the elderly. Additionally, Finns' average height has increased by almost 5 cm from the 1980s. The current lung volume in the Finnish population appears larger than predicted values according to GLI, thus strengthening the need for revised Finnish national reference values, presented by Kainu et al. in 2016. These values were determined from a sample of 1000 native, non-smoking Finns aged 18 to 83 using LLN and categorizing the degree of obstruction according to GLI [57,58,61,63,64].

2.4 OBSTRUCTION AND COMORBIDITIES

Comorbidities such as cardiovascular diseases, osteoporosis, and depression have association with COPD and diminish the quality of life. This has also been defined as multi-morbidity. Many of these comorbidities share risk factors with COPD, including an increasing age, smoking, and being male. The number and severity of comorbidities typically increases as COPD progresses, and comorbidities increase mortality among subjects with COPD. Moreover, many subjects die from diseases other than COPD, whereby the other primary causes of death are cardiovascular diseases, cancers, and other respiratory diseases [1,8,9,12,13,17,19,21,54,65].

2.5 OBSTRUCTION AND ALL-CAUSE MORTALITY

Smoking was found to have association with lung cancer as early as the 1950s, and COPD and a decreased lung function (decreased FEV₁) with all-cause mortality in the late 1980s and 1990s, an association strengthened in subsequent studies. All-cause mortality increases as COPD progresses and lung function decreases, particularly in current smokers but also in never-smokers. Both of the most commonly used definitions for obstruction (GOLD staging and LLN) predict mortality based on decreasing lung function [1,15-17,19,66-71]. The most significant factor explaining the association between reduced FEV₁ and all-cause mortality appears to be inflammatory markers, followed by coronary heart disease, stroke, and diabetes, and further by alcohol consumption, diet, physical activity, and BMI in a model adjusted for age, sex, and smoking [72].

2.6 OBSTRUCTION AND CARDIOVASCULAR COMORBIDITIES AND MORTALITY

Previous studies found associations between COPD and cardiovascular diseases in general and specifically with hypertension, coronary heart disease, heart failure, arrhythmias, peripheral vascular disease, and hypertension. However, previous studies on COPD and stroke showed both an association and no association [1,8,9,11-13,19,73-75].

Both, COPD and cardiovascular diseases predict all-cause mortality [1,13,18,24,65]. The association between COPD and decreased FEV₁ and cardiovascular mortality was demonstrated in large population-based studies published over 10 years ago. COPD predicts cardiovascular mortality in models adjusted for general cardiovascular disease risk factors and in studies with a long-term follow-up. In general, mortality increases as lung function decreases [11,13,18,65,76].

2.7 OBSTRUCTION AND ACUTE MYOCARDIAL INFARCTION (MI) AND CORONARY MORTALITY

Studies about the association between COPD and coronary mortality as well as MI are presented in Tables 1 and 2. According to these studies, COPD appears to have an association with coronary mortality in multivariate adjusted analyses, in studies among subjects without a baseline cardiovascular disease, in long-term follow-up studies, and in both sexes [11,15,18,22,77-80]. COPD and MI had an association in two previous studies among subjects without a baseline cardiovascular disease. Yet, cross-sectional and other

follow-up studies found both an association and no association between COPD and MI [11,22,74,78,81-87].

Table 1 Studies about COPD and coronary mortality

Country [reference]	Study name, research design, follow-up time	Population N / n ¹	Definition of COPD and others	Measured result	Result	Adjustments
Cardiovascular		excluded from the	study population			
USA [11]	Kaiser Permanente Medical Care Program, a case-control follow-up study, follow-up time 2.75 y	91 932 / 45 966 (55.4%), age \geq 40 y	COPD: register data; MI mortality: hospital discharge register	Risk for MI death in subjects with COPD	HR (95% CI): 1.85 (1.55–2.21)	Age, sex, hypertension, hyperlipidemia, diabetes
Cardiovascular		included in the	study population			
International multicenter study [22,78]	ECLIPSE, longitudinal prospective case-control study, follow-up time 3 y	2746 / 2180 GOLD stages 2–4 (65%), controls: 343 smokers (55%), 223 non-smokers (38%); age 40–75 y	COPD: spirometry, FEV ₁ /FVC < 0.7, GOLD stages 2–4; MI ² : self-reported	All-cause mortality in MI and COPD	HR (95% CI): 1.5 (1.1–2.0)	Age, sex, smoking
Denmark [15]	Copenhagen City Heart Study, a longitudinal study for a cohort, follow-up time 16–21 y	10 457 / 1915 (51.6%), mean age 52 y	COPD: spirometry, FEV ₁ /FVC < LLN; coronary death: register data	Coronary mortality in subjects with FEV ₁ < LLN compared to FEV ₁ \geq LLN first quartile	1. HR (95% CI): men 3.7 (2.3–6.0), women 11.1 (5.2–23.6) 2. HR (95% CI): baseline age \leq 45 y 4.4 (1.4–14.2) and > 45 y 5.5 (3.6–8.4)	Age, height

USA [79]	Rochester epidemiology project, a follow-up study for a cohort, follow-up time 28 y	3438 / 415 (58%), mean age 68 y	COPD: medical records; MI: hospital discharge register	Risk for all-cause mortality in subjects with MI and COPD	HR (95% CI): 1.3 (1.1–1.5)	Age, sex, smoking, hypertension, comorbidity, medications, reperfusion / revascularization
International multicenter study [77,80]	VALIANT trial, a follow-up study for a cohort, follow-up time 2 y	14 703 / 1258 (8.6%), age: COPD 68 y, no COPD 65 y	COPD: questionnaire; MI: hospital discharge register	Cardiovascular death after MI in subjects with COPD	HR (95% CI): 1.04 (0.92–1.19)	Age, blood pressure, smoking, diabetes, dyslipidemia, etc.
USA [11]	Kaiser Permanente Medical Care Program, a case–control follow-up study, follow-up time 2.75 y	91 932 / 45 966 (55.4%), age ≥ 40 y	COPD: register data; MI mortality: hospital discharge register	Risk for MI death in subjects with COPD	HR (95% CI): 1.81 (1.54–2.12)	Age, sex, hypertension, hyperlipidemia, diabetes
USA [18]	NHANES I 1971–1975, a follow-up study for a cohort, follow-up time 17–21 y	1861 (47.1%), FEV ₁ in quintiles, age 40–60 y at baseline, 123 coronary deaths during a follow-up period	COPD: spirometry data; coronary mortality: register data	1. Coronary mortality according to FEV ₁ in quintiles, comparing the highest quintile with the lowest 2. Same analysis for non-smokers	RR (95% CI): 5.65 (2.25–14.13) RR (95% CI): 3.98 (1.29–12.23)	Age, smoking, sex, diabetes, blood pressure, hyperlipidemia, BMI, race

¹ Total population/ COPD (% men), age in years.

² Acute myocardial infarction.

Table 2 Studies about COPD and acute myocardial infarction (MI)

Country [reference]	Study name, research design, follow-up time	Population N / n'	Definition of COPD and others	Measured result	Result	Adjustments
Cardiovascular		baseline excluded	from the study	population		
UK [81] ²	A case-control follow-up study, 10 y	71 544 / 35 772 (51%), age 40–79 y	COPD, MI: register data	Risk for MI in subjects with COPD	OR (95% CI): 1.40 (1.13–1.73)	Smoking, BMI, hypertension, hyperlipidemia, diabetes, NSAID use
USA [11]	Kaiser Permanente Medical Care Program, a case-control follow-up study, follow-up time 2.75 y	91 932 / 45 966 (55.4%), age ≥ 40 y	COPD: register data; MI: hospital discharge register	Risk for MI in subjects with COPD	HR (95% CI): 1.87 (1.69–2.08)	Age, sex, hypertension, hyperlipidemia, diabetes.
Cardiovascular		baseline included	in the study	population		
Spain [82]	A cross-sectional case- control study	304 / 204 coronary heart disease (84%), 100 controls (83%), mean age: case 67 y, controls 64 y	COPD: spirometry, FEV ₁ /FVC < 0.7; coronary heart disease: clinical diagnosis	COPD prevalence in subjects with ischemic heart disease	OR (95% CI): 1.19 (0.57–2.29)	Age, hypertension, sex, smoking, BMI, abdominal perimeter, dyslipidemia
USA [11]	Kaiser Permanente Medical Care Program, a case-control follow-up study, follow-up time 2.75 y	91 932 / 45 966 (55.4%), age ≥ 40 y	COPD: register data; MI: hospital discharge register	Risk for MI in subjects with COPD	HR (95% CI): 1.89 (1.71–2.09)	Age, sex, hypertension, hyperlipidemia, diabetes

International study [22,78]	ECLIPSE, a non-interventional cross-sectional study for a cohort	2746 / 2180 (65%), controls: 343 smokers (55%), 223 non-smokers (38%), age 40–75 y	COPD: spirometry, FEV ₁ /FVC < 0.7, GOLD stages 2–4; MI: self-reported in questionnaire	1. MI prevalence in subjects with COPD 2. Angina pectoris prevalence in subjects with COPD	Significantly increased prevalence Increased, significantly in GOLD stage 2	
Denmark [75]	Copenhagen City Heart Study, part IV, a cross-sectional study for a cohort	5890 / GOLD stage 1: 334 (49%), GOLD stage 2: 554 (47%), GOLD stages 3–4: 148 (48%), mean age 57 y (no COPD), 70 y (GOLD stages 3–4)	COPD: spirometry, FEV ₁ /FVC < 0.7, GOLD stages 1–4; coronary heart disease: hospital discharge register, EKG	Risk for previous MI in subjects with COPD	OR (95% CI): GOLD stages 1, 2, 3–4: 0.3 (0.1–0.8), 1.3 (0.8–1.9), 1.4 (0.7–2.8)	Age, sex
UK [83]	A case-control follow-up study, follow-up time 5 y	18 035 / 1927 (NS ³), mean age: case 67 y, controls 64 y	COPD, MI: register data	Risk for MI in subjects with COPD	RR (95% CI): 1.18 (0.81–1.71)	Age, sex
Denmark [84]	A case-control follow-up study, follow-up time 27 y	7 419 791 / 313 958 (50%), entire Danish population	COPD, MI: register data	Risk for MI in subjects with COPD	OR (95% CI): 1.27 (1.26–1.28)	
UK [85]	A cross-sectional and follow-up study, follow-up time 895 d	1 174 240 / 29 870 (48.1%), age > 35 y	COPD, MI: register data	Risk for MI in subjects with COPD Risk for MI in subjects with COPD aged 35–44 y	HR (95%CI): 3.53 (3.02–4.13) HR (95% CI): 10.34 (3.28–32.60)	Sex, smoking Sex, smoking

Sweden [86]	A follow-up study for a cohort, follow-up time 3.5 y	6 794 690 / 51 348 (44.3%)	COPD, MI: register data	Risk for MI in subjects with COPD	HR (95% CI): 1.47 (1.41–1.55)	Age, sex, socioeconomic status, cardiovascular and respiratory medications
Sweden [87]	OLIN, a cross-sectional study for a cohort, random sample	642 / 90 (54%), age 22–72 y	COPD: spirometry, FEV ₁ /FVC < 0.7; MI: self-reported	Prevalence of coronary heart disease in subjects with COPD	OR (95% CI): 2.6 (1.1–6.1)	
USA [74]	NHIS, a cross-sectional case-control population survey	5 950 / 2 975 (46%), mean age: all 56.8 y, COPD 60.3 y	COPD, MI: self-reported	MI prevalence in subjects with COPD	1. OR (95% CI): 2.2 (1.7–2.8) 2. OR (95% CI): age 40–60 y, 2.8 (1.8–4.5); age > 60 y, 1.7 (1.3–2.4)	Sociodemographic status, health behavior, comorbidities Adjusted ³

¹ Total population/ COPD (% men), other (% men), age in years.

² At baseline excluded: congestive heart failure, deep vein thrombosis, MI, pulmonary embolism, transient ischemic attack, stroke, cancer, cardiac arrhythmia, HIV, drug abuse, and alcoholism.

³ Not reported.

2.8 TUBERCULOSIS

Tuberculosis is a bacterial disease caused by *Mycobacterium tuberculosis*. Worldwide one in three individuals has latent tuberculosis, defined as an immunological sensitization to mycobacterial proteins, although only 10% of those with latent infection ever develop active tuberculosis. Yet, 9 million active tuberculosis infections occur yearly. Globally tuberculosis is the ninth leading cause of death and the leading lethal infectious disease concentrated in middle- and low-income countries. It has associations with poverty, smoking, and undernutrition. Many noncommunicable diseases such as diabetes as well as environmental exposures predispose individuals to active tuberculosis. Co-infection with HIV and drug-resistance tuberculosis strain increase mortality. Yet, most deaths from TB remain preventable through early diagnosis and proper treatment [32,33,36,88].

2.8.1 OBSTRUCTION AND PULMONARY TUBERCULOSIS (TB)

COPD increases the risk for developing active TB, while treated active TB represents a risk for COPD. Yet, some previous case-control studies showed no association. The strength of the association between past TB and obstruction correlates with the incidence rates of TB and appears stronger in adults under 40. The loss of lung function continues years after TB treatment depending on the severity of disease [29,36-38,41-43,53,89]. A disease history of TB appears to be a significant risk factor for COPD in non-smokers in developing countries, and the disease differs from COPD caused by smoking [90,91].

An abnormal chest x-ray with cavitation, bronchiectasis, fibrosis, and pleural thickening is common after treated active TB [92]. A TB indicative scar on a chest x-ray and latent TB also have an association with COPD and obstruction [36,39-41,93,94]. A TB-indicative scar predicts a decreasing FEV₁ in never-smokers as well [39,41], although a TB disease history has a stronger association with obstruction compared to a TB-indicative scar [95].

COPD and past TB, defined as a TB disease history or a TB-indicative scar on a chest x-ray, have an association with multiple similar factors, such as smoking, poverty, undernutrition, ageing, and comorbidities. Researchers suspect the association between TB and COPD is bidirectional, for instance, with lung remodeling and an immunological mechanism, occurring independently of common risk factors [1,32,33,36-38,93,96].

2.8.2 OBSTRUCTION, PAST TB, AND ALL-CAUSE MORTALITY

COPD and active TB cause mortality [1,37,97,98]. Additionally, a TB-indicative scar on a chest x-ray and a TB disease history predict all-cause

mortality in long-term follow-up as well as TB disease history mortality in COPD [37,98,99]. COPD increases all-cause mortality during the first year following an active TB diagnosis, although subjects with COPD had more comorbidities than those without COPD [43].

2.9 LOW VITAMIN D STATUS

2.9.1 OBSTRUCTION AND LOW VITAMIN D STATUS

A low vitamin D status results from insufficient dietary intake and inadequate exposure to sunlight generally measured as the serum 25-hydroxyvitamin-D (25(OH)D) concentration—that is, a value <30 nmol/L indicates deficiency and <50 nmol/L insufficiency. The prevalence of vitamin D deficiency was 0.6% in Finland according to the Health 2011 Survey following the current vitamin D fortification policy. In comparison, prevalence was 13% in the Health 2000 Survey before dietary fortification began. Respectively, the mean 25(OH)D concentrations were 65.4 nmol/L in the Health 2011 Survey, 47.6 nmol/L in the Health 2000 Survey, and 43.4 nmol/L in men and 41.5 nmol/L in women, respectively, in the Mini-Finland Health Survey [28,34,35,100].

Vitamin D metabolism is complex and the link between vitamin D metabolism and COPD remains unconfirmed. It's suspected that a low vitamin D status plays a role in immune defense, airway remodelling, and inflammatory reactions in COPD [28,45,101-103]. A review article summarized the results of previous studies about the association between lung functions and vitamin D status, finding inconsistent conclusions across studies [28]. For instance, in the National Health Examination Survey (NHANES), researchers found a difference in the FEV₁ and FVC levels between the highest and lowest vitamin D status quintiles, although that difference diminished after adjusting for confounders [103]. In another study, a low vitamin D status had an association with COPD, correlating with the severity of COPD [102].

A low vitamin D status and COPD have associations with multiple similar factors, such as ageing, smoking, inactivity, staying indoors, a low socioeconomic status, and chronic diseases, which might confound the association [1,2,22,28,46,47]. Epidemiological data about the associations between COPD and a low vitamin D status remain limited [101].

2.9.2 OBSTRUCTION, LOW VITAMIN D STATUS, AND ALL-CAUSE MORTALITY

A low vitamin D status and COPD predicted all-cause mortality in follow-up studies, revealing an inverse association between mortality and lung function as well as vitamin D status [1,2,15,22,46,47,104-106]. However, only three previous studies evaluated the effect of a low vitamin D status on all-cause

mortality in subjects with COPD with a long-term follow-up, and in those no correlation emerged [105,107,108].

2.10 HEALTH EXAMINATION SURVEYS EXAMINING OBSTRUCTION

2.10.1 FINNISH SURVEYS

2.10.1.1 Mini-Finland Health Examination Survey

This doctoral study was based on the Mini-Finland Health Examination Survey, the first national health examination survey. It was carried out between 1978 and 1980 by the Social Insurance Institution. The survey aimed to produce extensive data in health, disease prevalence and incidence, and any factors having association with them. The study population represented the adult Finnish population aged 30 and older. As a result, a massive amount of data was collected from each study participant about, for instance, their disease history, disabilities, symptoms, socioeconomic status, occupation, and various behavioral factors [48,51,109].

The baseline examination was performed by a moving unit, the Mobile Clinic, in 40 areas, where local nurses first conducted home interviews. Personnel from the Social Insurance Institution's Mobile Clinic gathered all other data, such as various measurements, tests, serological determinations, spirometry, and a chest x-ray. Subjects with abnormal results were invited to participate in the second stage of the baseline examination, including a standard physical examination performed by a physician. The results from the survey and subsequent follow-up through record linkage to national registers have been reported in dozens of doctoral studies and more than 300 original articles [51,109].

2.10.1.2 Health 2000 Survey, Health 2011 Survey, and other surveys

The Health 2000 Survey was the next Finnish national health examination survey performed between 2000 and 2001 using similar objects and measurements to those in the Mini-Finland Health Survey. A sample of 10 000 subjects represented adult Finns aged 18 years and older. The Health 2011 Survey was a follow-up study to the Health 2000 Survey's sample, aged at that time 29 and older, with a new random sample of persons aged 18 to 28. The Health 2000 and Health 2011 surveys used comparable methods including spirometry [110,111].

Every fifth year between 1972 and 2012, the national FINRISK Study was carried out. FINRISK was a population study which collected data about risk factors for chronic, noncommunicable diseases. The FINRISK Study and the Health 2000 Survey were combined in 2017 to form a new population study (FinHealth Survey), which is planned for every fifth year. No spirometry was included in the FinHealth 2017 study, although it is hopefully planned for the FinHealth 2022 study [112,113].

2.10.2 SCANDINAVIAN HEALTH EXAMINATION SURVEYS

2.10.2.1 Obstructive Lung Disease in Northern Sweden (OLIN) Study, Sweden

OLIN Study is a large longitudinal population-based study. This study consists of data from a stratified or random sample of over 50 000 Swedish subjects ranging from children to the elderly living across Norbotten county in Sweden collected in several cohorts beginning in 1985. Health data were gathered through structured interview and examinations including spirometry [115-117].

2.10.2.2 Copenhagen City Heart Study (CCHS), Denmark

The longitudinal population-based CCHS study conducted from 1975, was primarily designed to study cardiovascular diseases, but later added on other issues such as pulmonary diseases. The first phase of CCHS included a random sample of 20 000 adult subjects from the Copenhagen city population. Data were collected through questionnaires and examinations including spirometry. In follow-up studies, the same population was invited to take part, while adding new samples from younger age groups [15,118].

2.10.2.3 The Nord-Trøndelag Health (HUNT) Study, Norway

HUNT Study is a large population-based Norwegian cohort study consisting of 125 000 participants. Every subject aged 20 or older from Nord-Trøndelag County in Norway was invited to take part in the HUNT1, HUNT2, and HUNT3 studies performed between 1984 and 1986, 1995 and 1997, and 2006 and 2008. Spirometry was performed for a subgroup of the HUNT2 and HUNT3 samples [119].

2.10.3 OTHER COUNTRIES AND INTERNATIONAL SURVEYS

2.10.3.1 National Health Examination Survey (NHANES) in USA

NHANES has been performed in the USA since the early 1960s through various schemes. From 1999, about 5000 subjects have been examined annually in a nationally representative population sample across the USA. NHANES collects comprehensive health data through questionnaires, interviews, and examinations, including spirometries for part of the sample [115,120,121].

2.10.3.1 Framingham Heart Study

The Framingham Heart Study is a population-based cohort study originally among 5209 participants aged 28 to 62 established in 1948 in Framingham, MA, USA. After the original cohort, data were collected from new cohorts [122,123].

2.10.3.2 The Burden of Obstructive Lung Disease (BOLD) Study

BOLD Study is a multicenter international study which collects country-specific data about COPD from subjects aged 40 and older via questionnaires and spirometry [2,42,44].

2.10.3.3 The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) Study

PLATINO Study was a population-based, two-phase study that collected data from adults aged 40 or older in five urban areas in Latin America. Five centers participated during the baseline study in the first phase carried out between 2002 and 2004 (5315 participants). The follow-up study was performed in three centers 5 to 9 years from the baseline study for the first- phase participants. Health data were collected and spirometry was performed [106].

3. AIMS

This doctoral study aimed to assess baseline cross-sectional associations between obstruction and various factors, to control for those associations, and to evaluate whether obstruction predicts all-cause and cause-specific mortality and MI during a three-decade follow-up period in a national health examination survey representing adult Finns.

The specific aims in studies I to IV were as follows:

1. According to previous data, obstruction predicts all-cause mortality by decreasing lung function. Our research aimed to determine whether all-cause mortality in subjects with obstruction varied by GOLD stage, age, or sex in a long-term follow-up (study I).
2. Obstruction appears to predict cardiovascular mortality, yet many factors confound the association. In this study, we aimed to evaluate whether the GOLD stage or including only those who had no cardiovascular disease at baseline affected the association (study I).
3. Obstruction appears to predict coronary death, but previous studies found both positive and negative results about the association between obstruction and MI. Our research aimed to determine whether obstruction predicts MI and coronary death in a study population without a cardiovascular disease at baseline, and whether age, sex, or follow-up time affects the associations (study II).
4. Past TB and obstruction have an association with one another. However, only limited long-term follow-up data about whether past TB confounds or modifies the association between obstruction and all-cause mortality. We aimed to evaluate these associations (study III).
5. A low vitamin D status and obstruction appear to have an association with one another, and both predict premature mortality. This study aimed to determine whether a low vitamin D status confounds or modifies the association between obstruction and all-cause mortality (study IV).

4 MATERIALS AND METHODS

4.1 STUDY POPULATION

The Mini-Finland Health Survey was a national health examination survey carried out between 1978 and 1980. During the first stage of sampling, 320 clusters (including one or more municipalities) were combined to form 40 nationally representative areas (including one or more clusters) with 40 000 to 60 000 subjects living within them. The criteria for stratification included the proportion of industrial and agricultural populations and the population center degree. During the second stage, a systematic sample of 8000 subjects (3637 men and 4363 women) was drawn from the areas from the Social Insurance Institution's population registry, where each individual in the population had an equal probability of selection. The sample represented the Finnish adult population aged 30 or older. During the baseline survey (in 1978–1980), 7217 subjects participated (90.2% of the sample, 3322 men and 3895 women). The geographical location of study subjects in the baseline survey appears in Figure 2 [48,50,51,109].

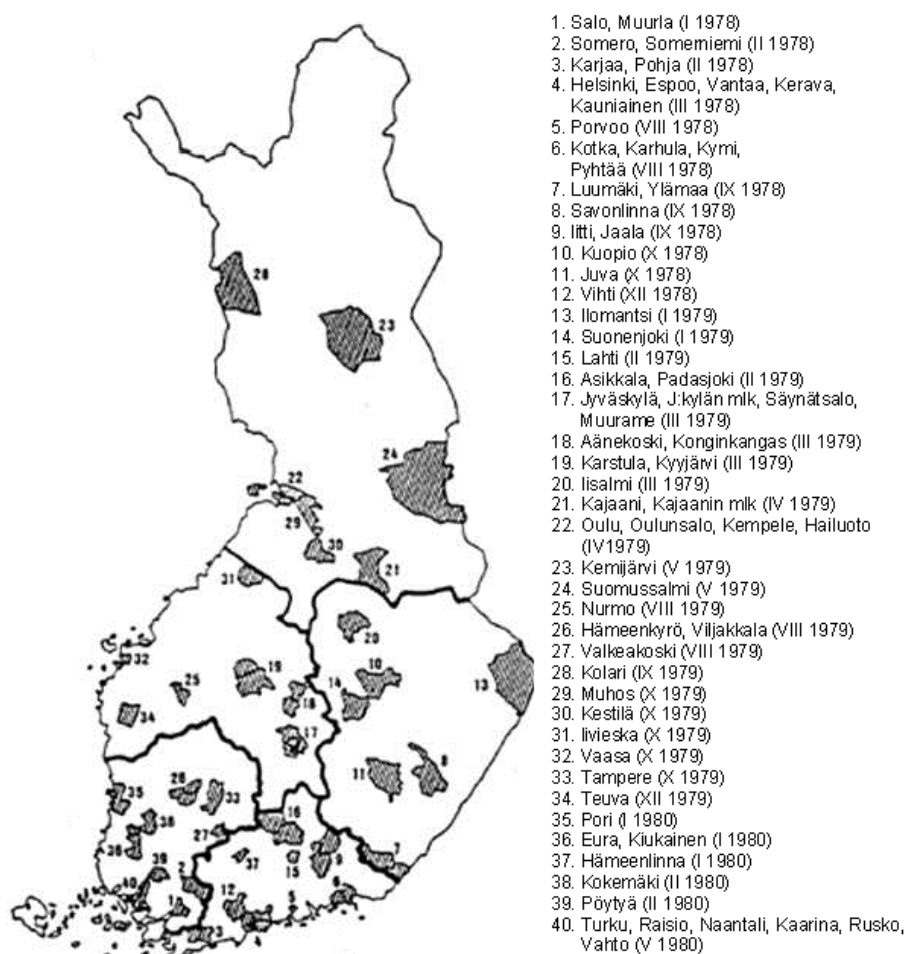


Figure 2 Geographical location of the Mini-Finland Health Survey study subjects

4.2 SELECTION OF SAMPLE POPULATIONS IN STUDIES I TO IV

In studies I to IV, we included those subjects for whom all the necessary data were collected for each study, including spirometry. Subjects with any missing data were excluded separately from each study. In addition, subjects with asthma were excluded from studies I and III. In study II, we aimed to determine whether obstruction at baseline represented an etiological factor for

MI or coronary death, and respectively, in the subanalyses for study I whether obstruction represented an etiological factor for cardiovascular mortality. Therefore, those with diagnosed cardiovascular disease (any heart disease, intermittent claudication, or cerebrovascular disease) at the baseline study were identified as possible confounders and excluded from those analyses. Figure 3 provides a flowchart of the study population in studies I to IV [50,51].

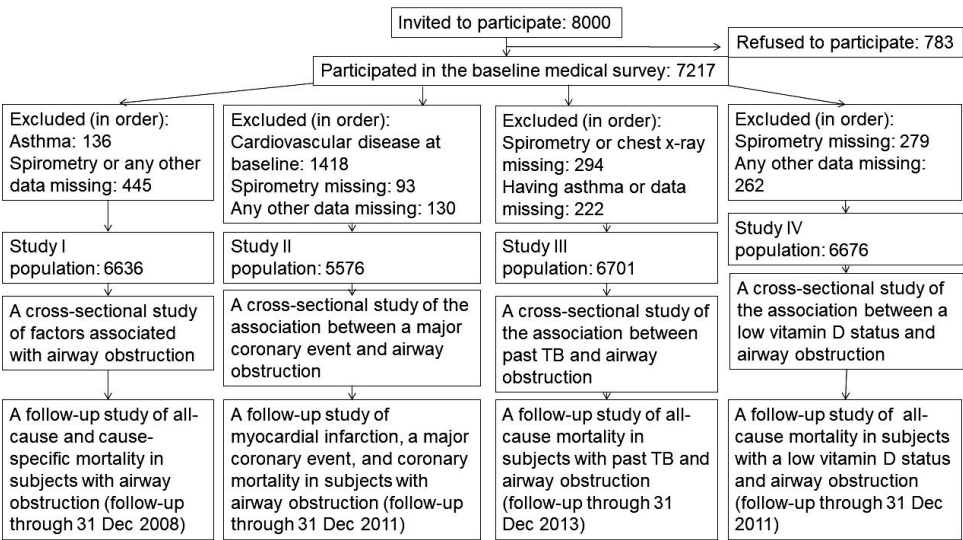


Figure 3 Flowchart of the study populations in studies I to IV

4.3 METHODS

4.3.1 BASELINE EXAMINATION

A baseline examination elicited the subject’s pertinent health information and consisted of a health interview, questionnaires, and a basic health examination including laboratory tests and various measurements, such as, blood pressures, chest x-ray, and spirometry [48,50,51,109].

4.3.2 STANDARD INTERVIEW, BASIC QUESTIONNAIRE, AND MEASUREMENTS

The basic questionnaire provided information on the subject’s general health, leisure physical activity, and educational level. General health was categorized

as good, moderate, or poor. Leisure physical activity was assessed using questions about the duration, intensity, and frequency of physical activity and further classified into three categories: inactive (little physical exercise), occasionally active (exercise during some hobbies or irregular exercise), or regularly active (regular exercise). Educational level was categorized according to the number of completed years of schooling: basic (< 8 years), intermediate (8–12 years), and higher (> 12 years).

Height, weight, and blood pressure were measured and an electrocardiogram (EKG) was taken using a standardized methodology. BMI (weight (kg)/height² (m²)) was calculated as a measure of relative weight [48,50,51].

Chest radiographs with anteroposterior and lateral views were taken in a mobile unit at a constant 120 kilo-voltage power, using automatic exposure control, and a 135-cm film focus. The chest radiograph was repeated later if the technical quality was low [50].

Smoking habits were assessed during a standard interview and study subjects were categorized as never-smokers, former smokers, and current smokers. Former smokers had quit smoking at least one month preceding the baseline survey. Current smokers smoked at least one cigarette, cigar, or pipe daily or almost daily during the last year prior to the survey. Current smokers were further divided into two groups according to daily smoking behavior: 1 to 19 and ≥ 20 cigarettes per day [50,51].

4.3.3 LABORATORY MEASUREMENTS

Fasting blood samples were taken during the baseline health examination and kept frozen at -20°C until measurement. The plasma glucose concentration was determined from blood samples and measured using the glucose oxidase method (Boehringer Mannheim, GmbH, Mannheim, Germany). The total serum cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were analyzed using a direct modification of the Liebermann–Burchard method [35,50,51]. The concentration of HDL cholesterol was measured from the supernatant of the serum after precipitation of low-density lipoprotein cholesterol (LDL) and very LDL cholesterol using a magnesium/dextran sulphate [124].

Vitamin D status was determined as the serum 25(OH)D concentration using radioimmunoassay (DiaSorin, Inc., Stillwater, MN, USA) in 2003. The inter-assay coefficient of variation for 25(OH)D determination was 7.80% at a mean level of 47.3 nmol/L ($n = 167$) and 9.12% at the level of 131.3 nmol/L ($n = 135$). The proportion of quality-control samples was 13.5% [35,125]. For analyses, we used the tertiles of the measured 25(OH)D concentrations: 5 to 32 nmol/L, 33 to 48 nmol/L, and 49 to 180 nmol/L. There was no specifically determined concentration for a low vitamin D status.

The C-reactive protein (CRP) was determined between 2003 and 2005 using a latex turbido-metric immunoassay (Olympus AU 400 analyzer system

for clinical chemistry, Wako Chemicals, Neuss, Germany). The detection limit for CRP was 0.06 mg/L. The measured levels of CRP were categorized for analyses in this study as follows: 0.04 to 0.99 mg/L, 1.00 to 1.99 mg/L, and \geq 2.00 mg/L [50,51].

4.3.4 SPIROMETRY

Spirometry was performed in the Mini-Finland Health Survey to screen for abnormal lung functions and to categorize lung functions according to the measured values. The requirements for the spirometry device in the health examination survey were that it should be reliable, simple to use, fast, strong, light, and in common use. The Vitalograph spirometer (Vitalograph Ltd., Buckingham, England) having the best correspondence with these criteria, was used in the study [50,126].

Spirometry was performed at the baseline according to the manufacturer's guidelines. The measurement quality was controlled during the study. Laboratory technicians were specially trained to perform spirometry to ensure the quality. The technicians followed the standard guidelines and instructions for spirometry, and presented the test procedure individually to each subject. The intention was to record for each participant at least two spirometry curves, which were as consistent as possible. Subjects were instructed to inhale and fill their lungs with air, and, then, to exhale as forcefully and completely as possible to reach an adequate and high-quality forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC).

The highest technically acceptable efforts recorded for the body temperature and pressure, saturated with water vapor (BTPS) values of FEV₁ and FVC were reported and FEV₁/FVC was estimated by using the highest FEV₁ and FVC readings. No bronchodilation was performed [50,51,59,127].

4.3.5 STANDARDIZED PHYSICAL EXAMINATION

The basic questionnaire included questions about the symptoms of chronic disease, a history of any chronic disease diagnosed by a physician, the overall health status, and lifestyle factors. Those with any abnormal findings from the questionnaires or basic examination were advised to participate in a standardized physical examination performed by a specially trained physician [48,50,51].

4.4 DEFINITION OF DETERMINANTS

4.4.1 REFERENCE VALUES FOR OBSTRUCTION

In studies I to III, the individual results for each subject were calculated according to SAPALDIA. In subjects older than 75, the statistical formulae for the SAPALDIA reference values biased the values [56,62]. Therefore all such subjects were assumed to be 75 years old in the statistical formulae. In studies II and IV, obstruction was determined using the international GLI reference values based on the values for Caucasians [58].

4.4.2 CLASSIFICATION OF OBSTRUCTION

Four different definitions for obstruction were used in studies I to IV: those with a fixed cut-off limit ($FEV_1/FVC < 0.7$) and with either GOLD stages 1–4 (study I) or GOLD stages 2–4 (study I) or with $FEV_1/FVC < LLN$ according to SAPALDIA (studies I and III) or GLI (studies II and IV), categorized as having an obstruction; all others did not [1,3]. The LLN categorization for each subject was calculated using an individual LLN value for obstruction corresponding to the age, sex, and height of the subjects [56,58]. In studies I and III, the degree of obstruction was further classified into GOLD stages 1–4 (Figure 1, Table 3) [1,3].

4.4.3 CARDIOVASCULAR DISEASES, DIABETES, AND ASTHMA

A field physician diagnosed cardiovascular diseases, diabetes, and asthma on the basis of all available information; therefore, no data were missing for the diabetes and baseline cardiovascular disease categories for any subjects. In studies I and II, the category of baseline cardiovascular disease included any diagnosed heart disease, intermittent claudication, or cerebrovascular disease [50]. Subjects were determined to have diabetes if they had a self-reported history of diagnosed diabetes and were treated by a physician for diabetes, if they had a fasting plasma glucose level ≥ 6.7 mmol/L, or both [48,50,51]. Asthma was indicated if a physician previously diagnosed asthma, if the subject received medication for asthma, or if the subject was under current physician treatment for asthma [3,48,50,51].

4.4.4 PAST TB

In this study, only past pulmonary tuberculosis (TB) was analyzed. The basic questionnaire elicited TB history through the following questions: “Have you had, according to a physician’s diagnosis, pulmonary (lung) TB? Have you ever been hospitalized for it? Have you ever received medications for it [50]?”

Chest x-rays were taken during the baseline survey in a transferable radiological unit of the Mobile Clinic at all 40 study places and analyzed by two experienced radiologists who assessed independently of each other the scars or local fibrosis representing earlier TB on a chest x-ray. The computed kappa coefficient for the radiologists' diagnostic agreement among subjects without a TB disease history was 0.49 [95% confidence interval (95% CI) 0.45–0.52, McNemars' s test for systematic difference, $p = 0.0026$] [48,50,128].

According to this data, past TB was categorized hierarchically as: a TB indicative scar on a chest x-ray identified by one or both radiologists (no TB treated in hospital and no history of TB medications), a disease history (TB treated in hospital or with TB medications), past TB (either a TB disease history or a radiological scar), and no TB. The category of no TB included subjects with neither a TB disease history nor a scar on a chest x-ray.

4.5 FOLLOW-UP

After the baseline examination, it was possible to follow the study population through various registers using the subject's social security number to track participants. For this study, the study population's register data were continuously followed-up through Statistics Finland (causes of death, Study I–IV) and through the Hospital Discharge Registers (Study II) [49,129].

Mortality in the cohorts was followed for studies I to IV from Statistics Finland using the subjects' individual identification numbers to track participants according to the eighth, ninth and tenth editions of the *International Classification of Diseases* (ICD-8, ICD-9, and ICD-10, respectively) based on the baseline examination through 31 December 2008 in study I, 2011 in studies III and IV, and 2013 in study II [49]. In studies I through IV, all-cause mortality included all deaths in the study population during the follow-up periods.

In study I, outcomes from cardiovascular mortality included coronary heart disease (ICD codes 410–414 in ICD-8 and ICD-9 and I20–I25 in ICD-10) and cerebrovascular deaths due to subarachnoid hemorrhage (430 in ICD-8 and ICD-9 and I60 in ICD-10), hemorrhagic stroke (431 in ICD-8 and ICD-9 code and I61 in ICD-10), ischemic stroke (433–434 in ICD-8 and ICD-9 codes and I63 in ICD-10), or other unspecified cerebrovascular causes (435–438 in ICD-8, 432 and 435–438 in ICD-9, and I62 and I64–I69 in ICD-10).

In study II, subjects were followed for three different endpoints (until any of the following occurred first): date of hospitalization for MI, death, or through 31 December 2013. Diagnoses for hospital care periods were followed from the National Care Register for Health Care according to ICD-8, ICD-9, and ICD-10, respectively. This registry is a nationwide obligatory automated database containing the hospital discharge diagnosis codes for all medical admissions maintained by the Finnish National Institute for Health and Welfare [49,129].

In study II, the endpoint of MI included hospital care periods registered using ICD codes 410 (ICD-8 and ICD-9) and I21 and I22 (ICD-10). A major coronary event necessitating hospital care periods registered using ICD codes 410 and 411.0 (ICD-8 and ICD-9) and I20.0, I21, and I22 (ICD-10), undergoing coronary artery bypass graft surgery (CABG) or angioplasty, or the cause of death listed by using ICD codes 410–414 and 798 (but not 798.oA) (ICD-8 and ICD-9) and I20–I25, I46, R96, and R98 (ICD-10) were included. Coronary death in study II included cause of death registered using ICD codes 410–414 and 798 (but not 798.oA) (ICD-8 and ICD-9) and I20–I25, I46, R96, and R98 (ICD-10).

The long-term persistence of obstruction was analyzed among 905 participants from the baseline Mini-Finland Health Survey who were re-examined at the next national health examination survey, Health 2000 [111]. According to the fixed cut-off limit ($FEV_1/FVC < 0.7$), 12 subjects had obstruction at baseline; after 21 to 23 years, 9 of these had persistent obstruction, while 3 did not.

4.6 MODELS

The models were constructed based on previous studies, the aims of each study, and our research group's analyses of the Mini-Finland Health Survey data.

Obstruction at baseline was examined by predicting the all-cause, cardiovascular (study I) and coronary mortality, respectively, and MI and a major coronary event (MI or coronary mortality, whichever occurred first) (study II). Factors which had shown an association with cardiovascular diseases in previous studies were entered into multivariate models as potential confounders: age, sex, smoking, BMI, educational level, leisure physical activity, general health, diabetes, diastolic and systolic blood pressure, and serum total and HDL cholesterol concentrations.

Study III focused on the associations between obstruction, past TB, and all-cause mortality. Multivariate models were adjusted for those factors which had shown associations with obstruction, past TB, and all-cause mortality in previous studies or in the current study. Factors such as age, sex, smoking, BMI, general health, leisure physical activity, and educational level were included in the model. Past TB was also analyzed as a potential effect modifier.

In study IV, our research group evaluated the associations between obstruction, a low vitamin D status, and all-cause mortality. Multivariate models were adjusted for factors which had shown an association with obstruction, vitamin D status, and all-cause mortality in previous studies [35,130,131] or in the current study. Factors such as age, sex, smoking, educational level, leisure physical activity, BMI, CRP, and asthma were included. Vitamin D status was also analyzed as a potential effect modifier.

4.7 STATISTICAL METHODS

Cross-sectional associations between obstruction and various baseline characteristics were analyzed through logistic regression. The results were expressed as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). The Cox's proportional hazards regression model was used to estimate the strength of the association between obstruction and various endpoints during follow-up. The adjusted hazard ratios (HRs) with 95% CIs were estimated. Two main models were constructed in studies I to IV: adjusted for age and sex (and in some cases, for smoking as well, model 1) and adjusted for factors considered potential confounders in each study (a multivariate model, model 2). In this thesis, the most important results are reported from the analyses including the entire study population or a specific subpopulation. The effect modification was studied by entering multiplicative first-degree interaction terms one-by-one into the Cox's model for each study. The statistical significance of the interactions was tested using a likelihood ratio test in studies I, III, and IV and with the Wald's test in study II. Analyses related to studies I, III, and IV were performed using SAS System for Windows (SAS Institute, Inc., Cary, NC, USA, versions 9.1, 9.2, and 9.3) and using IBM's SPSS (version 23 and 24) for studies II and IV.

4.8 ETHICAL CONSIDERATIONS

The Mini-Finland Health Survey predated current legislation on ethics in medical research. However, all participants were fully informed about the study, they participated voluntarily, and the use of their information for medical research was explained to them. Agreeing to participate in the baseline health examination was understood to indicate informed consent. Statistics Finland approved the linkage of national mortality data to the survey data used here [49].

According to a statement from the Medical Ethics Committee of the Hospital District of Helsinki and Uusimaa in Finland (June 2013), this doctoral study does not fall under the purview of laws regarding medical research. Thus, the study protocol does not violate any ethical considerations or standards.

5 RESULTS

5.1 OBSTRUCTION IN STUDIES I TO IV

Obstruction was determined in studies I to IV by applying two different reference values and the four definitions. The prevalence of obstruction at baseline varied from 3.4% to 4.7% (Table 3).

Table 3 *Prevalence of obstruction in study I to IV populations using different reference values and definitions of obstruction and the incidence of all-cause mortality in subjects with and without obstruction during various follow-up periods.*

	Follow-up time until	Reference values	Definition for obstruction	Total (n) ²	Death (n) ³
Study I	31 Dec 2008	SAPALDIA	FEV ₁ /FVC ≥ 0.7 or FEV ₁ /FVC < 0.7, GOLD 1	6338 (95.3%)	2895 (45.7%)
			FEV ₁ /FVC < 0.7, GOLD 2–4	298 (4.5%)	273 (91.2%)
			FEV ₁ /FVC < 0.7, GOLD 1	165 (2.5%)	133 (80.6%)
			FEV ₁ /FVC < 0.7, GOLD 2	213 (3.2%)	192 (90.1%)
			FEV ₁ /FVC < 0.7, GOLD 3	72 (1.1%)	68 (94.4%)
			FEV ₁ /FVC < 0.7, GOLD 4	13 (0.2%)	13 (100%)
			FEV ₁ /FVC ≥ LLN	6407(96.6%)	2981 (46.5%)
			FEV ₁ /FVC < LLN	231 (3.4%)	188 (81.3%)
			FEV ₁ /FVC < LLN, GOLD 1	46 (0.7%)	22 (47.8%)
			FEV ₁ /FVC < LLN, GOLD 2	108 (1.6%)	93 (86.1%)
			FEV ₁ /FVC < LLN, GOLD 3	65 (1.0%)	61 (93.8%)
			FEV ₁ /FVC < LLN, GOLD 4	12 (0.2%)	12 (100%)
Study II	31 Dec 2011	SAPALDIA	FEV ₁ /FVC ≥ LLN	5413 (97.1%)	2396 (44.3%)
			FEV ₁ /FVC < LLN	163 (2.9%)	121 (74.2%)
		GLI	FEV ₁ /FVC ≥ LLN	5366 (96.2%)	2366 (44.1%)
			FEV ₁ /FVC < LLN	210 (3.8%)	151 (71.9%)
Study III	31 Dec 2013	SAPALDIA	FEV ₁ /FVC ≥ LLN	6466 (96.5%)	3625 (56.1%)
			FEV ₁ /FVC < LLN	235 (3.5%)	199 (84.7%)
			FEV ₁ /FVC < LLN, GOLD 1	47 (0.7%)	24 (51.1%)
			FEV ₁ /FVC < LLN, GOLD 2	112 (1.7%)	101 (90.2%)
			FEV ₁ /FVC < LLN, GOLD 3	64 (1.0%)	62 (96.9%)
			FEV ₁ /FVC < LLN, GOLD 4	12 (0.2%)	12 (100%)
Study IV	31 Dec 2011	GLI	FEV ₁ /FVC ≥ LLN	6365 (95.3%)	3283 (51.6%)
			FEV ₁ /FVC < LLN	311 (4.7%)	247 (79.4%)

¹ Study populations were defined separately for studies I to IV including those with all necessary data for each study. From the study II population, subjects with a cardiovascular disease diagnosed at baseline study were excluded.

² Number and percentage of subjects with and without obstruction in study I to IV populations.

³ Number and percentage of subjects with and without obstruction who died during follow-up

The overlapping between obstruction and asthma was evaluated in the study II population using the SAPALDIA and GLI reference values. According to SAPALDIA, there were 163 subjects with only obstruction, 86 with only asthma (diagnosed at baseline), and 14 with both asthma and obstruction (Kappa 0.094). According to GLI, there were 191 subjects with only obstruction, 67 with only asthma, and 19 with both asthma and obstruction (Kappa 0.109). Using the GLI reference values in subjects aged 30 to 49, we identified 30 with only obstruction, 7 with asthma, and 3 with both asthma and obstruction (Kappa 0.018).

5.2 BASELINE CHARACTERISTICS IN THE MINI-FINLAND HEALTH SURVEY

The distributions of the baseline characteristics and the number of missing values among all 7217 subjects who participated in the baseline study appear in Table 4. No data were missing for age, sex, diabetes, and cardiovascular disease at baseline. Baseline characteristics for studies I to IV can be found in the articles attached at the end of this thesis.

Table 4 Baseline characteristics in the Mini-Finland Health Survey study population (*n* = 7217) and the number of subjects with missing values for each characteristic.

Characteristics	Mean and standard deviation (SD) or prevalence	Data missing
Age (years)	51.3, \pm 14.2	
Women	3322 (46.0%)	
Smoking		10
Never-smoker	3999 (55.5%)	
Former smoker	1505 (20.9%)	
Current smoker, 1–19 cigarettes/ day	1062 (14.7%)	
Current smoker, \geq 20 cigarettes/day	641 (8.9%)	
FEV ₁ /FVC (%) ¹	80.1, \pm 7.5	209
Asthma	136 (1.9%)	22 self-reported, 54 clinical diagnosis ²
General health		9
Good	3377 (46.9%)	
Moderate	2673 (37.1%)	
Poor	1158 (16.1%)	
Leisure physical activity		10
Inactive	2636 (36.6%)	
Occasionally active	3477 (48.2%)	
Regularly active	1094 (15.2%)	
Educational level		20
Basic (<8 years)	4885 (67.8%)	
Intermediate (8–12 years)	1506 (20.9%)	
Higher (>12 years)	806 (11.2%)	
Diabetes	412 (5.7%)	
BMI (kg/m ²)	25.9, \pm 4.1	13
Systolic pressure (mmHg)	146.4, \pm 24.0	6
Diastolic pressure (mmHg)	87.3, \pm 11.8	6
Fs-cholesterol (mmol/L)	7.0, \pm 1.4	3
Fs-HDL cholesterol (mmol/L)	1.7, \pm 0.4	6
Past TB ³		93
No TB	5836 (81.9%)	
One radiologist observed ³	652 (9.2%)	
Two radiologists observed ³	403 (5.7%)	
Disease history ⁴	233 (3.3%)	
Vitamin D status (nmol/L) ⁵	42.9, \pm 19.6	147
CRP (mg/L) ⁶	2.5, \pm 4.7	268
Baseline cardiovascular disease ⁷	1418 (19.7%)	

¹ FVC: mean 4.05, SD \pm 1.2, data missing for 205 subjects; and FEV₁: mean 3.3 l/s, SD \pm 1.0, data missing for 208 subjects.

² Number of subjects with missing data for a self-reported history of asthma and clinical diagnosis of asthma at baseline survey.

³ A scar or local fibrosis on a chest x-ray observed by one or both radiologists in the Mini-Finland Health Survey, excluding those with TB treated in hospital or prescribed TB medications.

⁴ TB treated in hospital or prescribed TB medications.

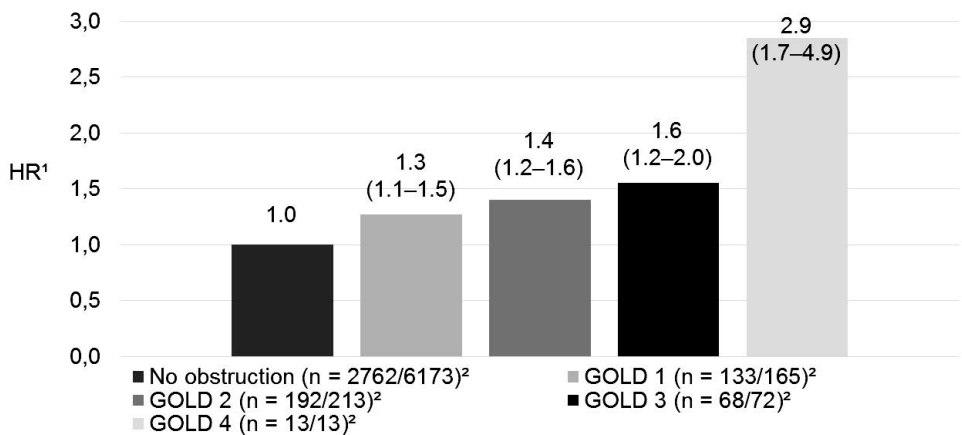
⁵ Concentration of 25(OH)D.

⁶ Concentration of serum C-reactive protein.

⁷ Subjects with any heart disease, intermittent claudication, or cerebrovascular disease diagnosed at baseline.

5.3 ALL-CAUSE MORTALITY, CAUSE-SPECIFIC MORTALITY, AND MI

We analyzed data for 6636 participants in study I and 5567 participants in study II where those with cardiovascular disease at baseline were excluded. Obstruction, with a increasing GOLD stage, predicted all-cause mortality during follow-up in study I (Figure 4).

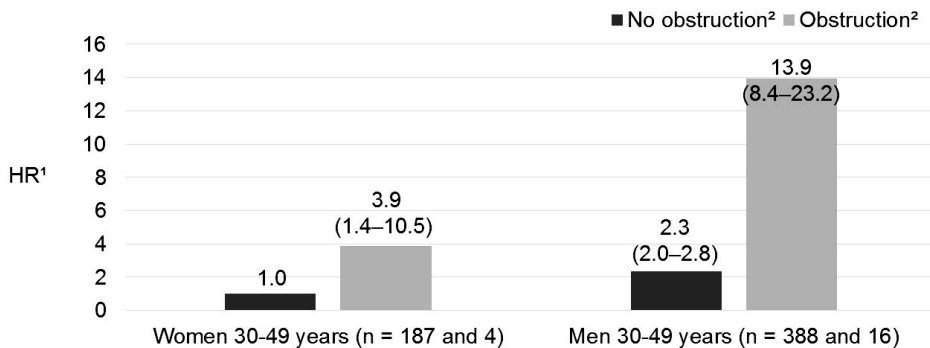


¹ Hazard ratios with 95% CIs for all-cause mortality adjusted for age, sex, and smoking. Those without obstruction were used as the reference.

² No obstruction was categorized as $FEV_1/FVC \geq 0.7$, while those with < 0.7 were further categorized as GOLD stages 1–4. The number of deaths relative to all cases appears in parentheses for each category.

Figure 4 Obstruction and all-cause mortality by GOLD stage 1–4 during follow-up from 1978–1980 through 31 December 2008.

Obstruction predicted all-cause mortality for both sexes in all age groups (30–49, 50–69, and ≥ 70 years), but the difference between subjects with and without airway obstruction was more pronounced in men and women aged 30 to 49 at baseline in study I population (Figure 5).



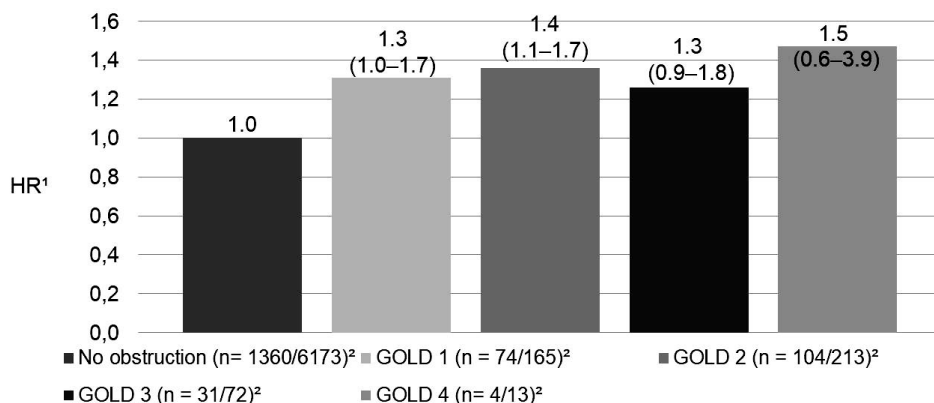
¹ Hazard ratios with 95% CIs in model adjusted for age and sex. Women aged 30–49 years without obstruction were used as the reference.

² No obstruction = $FEV_1/FVC \geq 0.7$ or $FEV_1/FVC < 0.7$ and GOLD stage 1; obstruction = $FEV_1/FVC < 0.7$ and GOLD stages 2–4.

³ The number of deaths in subjects without and with obstruction appears in parentheses.

Figure 5 Obstruction and all-cause mortality in women and men aged 30–49 at baseline in a follow-up study from 1978–1980 through 31 December 2008.

In study I, 1573 deaths (49.7% of all deaths) resulted from cardiovascular causes. We found a strong association between GOLD stage and cardiovascular mortality in an age-, sex-, and smoking (Figure 6) and in a multivariate adjusted model. Respectively, HRs with 95% CIs for GOLD stages 1 to 4 were 1.35 (1.06–1.72), 1.34 (1.09–1.65), 1.20 (0.83–1.72), and 1.27 (0.47–3.40) in a multivariate analysis when those without obstruction were used as the reference. Yet, we found no clear-cut association after those subjects with cardiovascular disease at baseline were excluded from the analysis. Respectively, HRs with 95% CIs from GOLD stages 1 to 4 in an age-, sex-, and smoking adjusted model were 1.22 (0.84–1.78), 1.46 (1.05–2.04), 1.49 (0.87–2.56), and 2.21 (0.31–15.85), and 1.32 (0.90–1.92), 1.34 (0.95–1.88), 1.37 (0.79–2.37), and 2.03 (0.28–14.67) in a multivariate adjusted model. Those without obstruction were used as the reference value. The multivariate model was adjusted for age, sex, smoking, general health, leisure physical activity, educational level, diabetes, BMI, total and HDL cholesterol, and systolic and diastolic blood pressure.

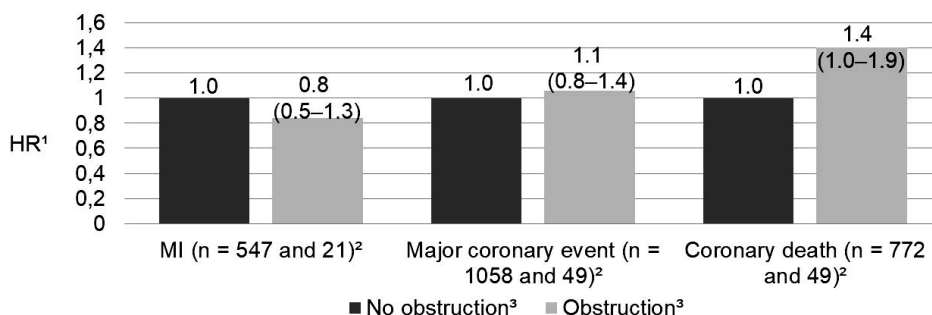


¹ Hazard ratios with 95% CIs for cardiovascular mortality in a model adjusted for age, sex, and smoking.

² No obstruction = $FEV_1/FVC \geq 0.7$; those with obstruction ($FEV_1/FVC < 0.7$) were further categorized in GOLD stages 1–4. Those without obstruction were used as the reference. The number of deaths due to cardiovascular disease relative to all cases appears in parentheses for each category.

Figure 6 Obstruction and cardiovascular mortality for GOLD stages 1–4 in a follow-up study from 1978–1980 through 31 December 2008.

Obstruction predicted coronary mortality, but not MI or a major coronary event in a multivariate model during follow-up for those without cardiovascular disease at baseline in the study II population (Figure 7).



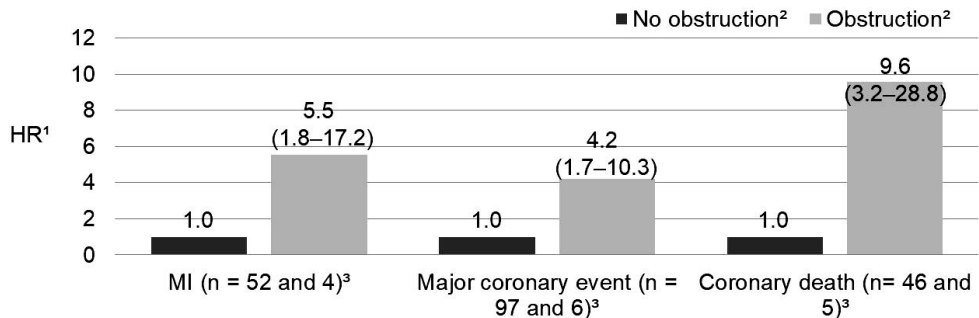
¹ Hazard ratios with 95% CIs in a model adjusted for age, sex, smoking, asthma, general health, leisure physical activity, educational level, BMI, diabetes, systolic and diastolic blood pressure, and the total and HDL cholesterol levels.

² The number of non-obstructive and obstructive subjects suffering MI, major coronary event, and coronary death appears in parenthesis for each category. A total of 5366 subjects had no obstruction and 210 had obstruction.

³ No obstruction = $FEV_1/FVC \geq LLN$; obstruction = $FEV_1/FVC < LLN$. Those without obstruction were used as a reference for each category.

Figure 7 Obstruction and MI, a major coronary event, and coronary death in a multivariate model among those without cardiovascular disease at baseline (n = 5567 subjects) from 1978–1980 through 31 December 2011.

Obstruction predicted MI, a major coronary event, and coronary death during follow-up in subanalysis among women aged 30 to 49 years at baseline in the study II population (Figure 8).



¹ Hazard ratios with 95% CIs in a multivariate model adjusted for age, smoking, asthma, general health, leisure physical activity, educational level, BMI, diabetes, systolic and diastolic blood pressure, and the total and HDL cholesterol levels.

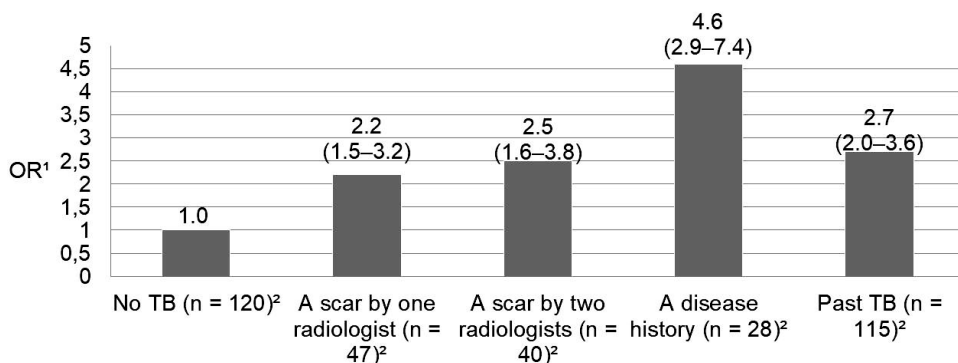
² No obstruction = $FEV_1/FVC \geq LLN$; obstruction = $FEV_1/FVC < LLN$. Those without obstruction were used as the reference.

³ The number of subjects with MI, major coronary event, and coronary death among those without and with obstruction appears in parentheses for each category.

Figure 8 Obstruction and MI, a major coronary event, and coronary death among women without diagnosed cardiovascular disease aged 30–49 at baseline in a follow-up study from 1978–1980 through 31 December 2011.

5.4 PAST TB AND ALL-CAUSE MORTALITY

Among 6701 subjects in study III, 1191 (17.8%) had past TB including a TB disease history or a TB indicative scar on a chest x-ray. In a cross-sectional study, those with past TB were more often former or current smokers, men, had a poorer general health, and a lower educational level compared to the entire study population. Past TB and obstruction had an association in a cross-sectional study, and none of the baseline characteristics modified the association between past TB and obstruction (Figure 9).



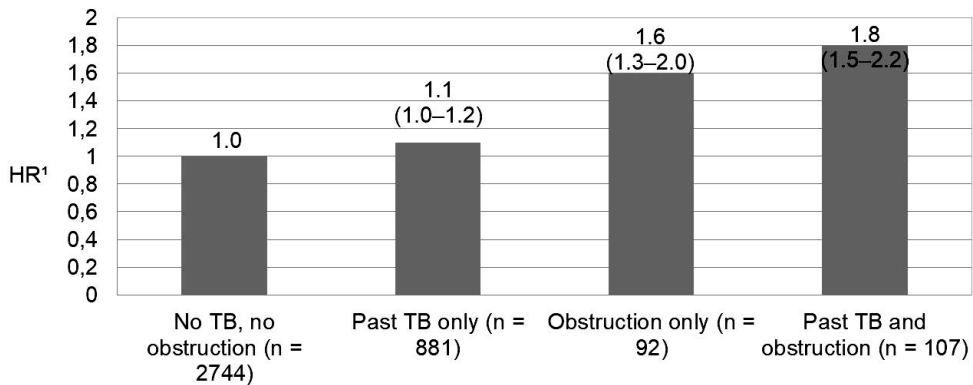
¹ Odds ratios with 95% CIs in a model adjusted for age, sex, smoking, BMI, physical activity, educational level, and general health. Obstruction categorized as $FEV_1/FVC < LLN$. Past TB including a scar on chest x-ray diagnosed by one or two radiologists or a disease history.

² The number of subjects on each category appears in parentheses.

Figure 9 The cross-sectional association at baseline between obstruction and TB history.

There were 3824 (57% of the population) deaths during the follow-up period. A TB disease history did not predict all-cause mortality, although scars observed on a chest x-ray and obstruction did, both independently of each other and independently of the confounding factors. HRs with 95% CIs for all-cause mortality among those with past TB reached 1.10 (1.00–1.21) in a multivariate model when a scar was noted by one radiologists, 1.17 (1.04–1.32) when noted by two radiologists, 1.01 (0.86–1.20) when there was a disease history, and 1.11 (1.03–1.20) when there was any past TB (those without TB were used as the reference value). A multivariate model was adjusted for age, sex, smoking, BMI, physical activity, education, and general health.

Past TB and obstruction had an additive joint effect on all-cause mortality (Figure 10). Neither past TB nor obstruction had a modifying or confounding effect on the association with the other for all-cause mortality.



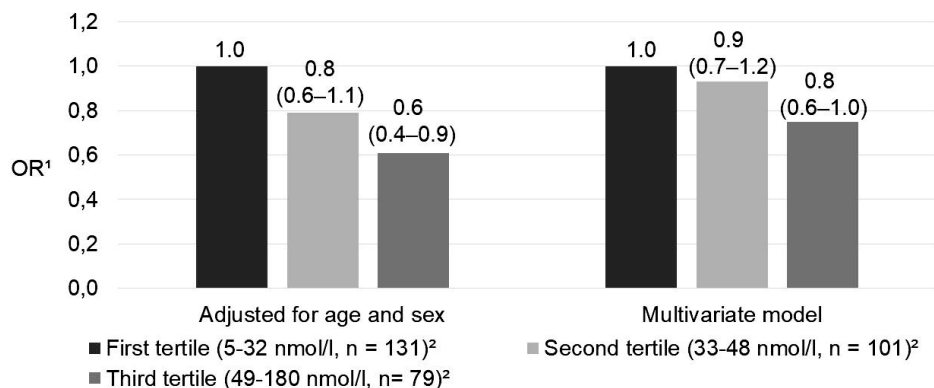
¹ Hazard ratios with 95% CIs in a model adjusted for age, sex, smoking, BMI, leisure physical activity, educational level, and general health.

² Past TB including a scar on a chest x-ray diagnosed by one or two radiologists or a disease history. Obstruction categorized as $FEV_1/FVC < LLN$. The number of subjects who died within each category appears in parentheses.

Figure 10 Joint effect of past TB and obstruction on all-cause mortality in a follow-up study from 1978–1980 through 31 December 2013.

5.5 VITAMIN D STATUS AND ALL-CAUSE MORTALITY

Study IV consisted of 6676 subjects. The mean 25(OH)D concentration was 43.4 nmol/L (SD ± 19.5) for the entire study population and 39.1 nmol/L (SD ± 18.8) among subjects with obstruction. We found a significant cross-sectional association between obstruction and a low vitamin D status at baseline in a model adjusted for age, sex, and smoking, but not in a multivariate model also adjusted for asthma, educational level, leisure physical activity, BMI, and CRP (Figure 11).

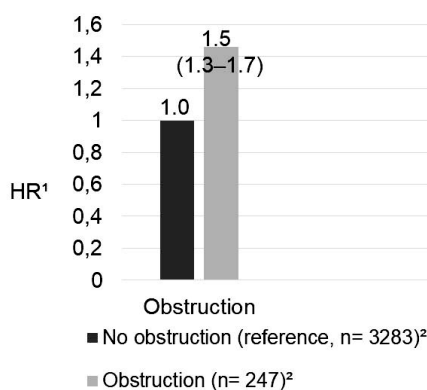


¹ Odds ratio with 95% CIs in a multivariate model adjusted for age, sex, smoking, asthma, leisure physical activity, educational level, BMI, and CRP. Those with the first tertile of vitamin D status were used as a reference. Obstruction categorized as $FEV_1/FVC < LLN$.

² The number of obstructive subjects within each category appears in parentheses.

Figure 11 Cross-sectional association at baseline between obstruction and vitamin D status.

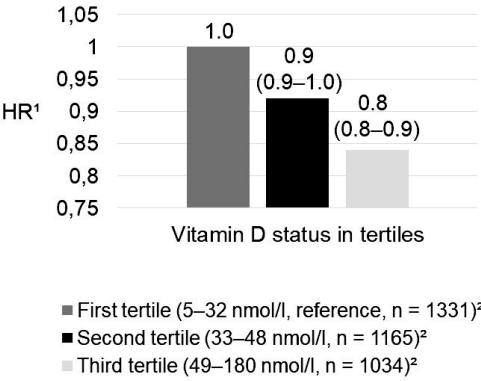
During follow-up, 3530 subjects (52.9% of the population) died. Obstruction and a low vitamin D status predicted all-cause mortality independently of each other in a multivariate model (Figures 12 and 13).



¹ Hazard ratios with 95% CIs in a multivariate model adjusted for vitamin D status, age, sex, smoking, asthma, leisure physical activity, educational level, BMI, and CRP. Obstruction categorized as $FEV_1/FVC < LLN$. Those without obstruction were used as the reference.

² The number of subjects who died within each category appears in parentheses.

Figure 12 The association between obstruction and all-cause mortality in a follow-up study from 1978–1980 through 31 December 2011.



¹ Hazard ratios with 95% CIs in a multivariate model adjusted for obstruction, age, sex, smoking, asthma, leisure physical activity, educational level, BMI, and CRP. The first tertile of vitamin D status was used as the reference.

² The number of subjects who died within each category appears in parentheses.

Figure 13 The association between vitamin D status and all-cause mortality in a follow-up study from 1978–1980 through 31 December 2011.

Vitamin D status did not affect the association between obstruction and all-cause mortality. Yet, a statistically significant interaction between obstruction and vitamin D status was found ($p = 0.007$). In subjects without obstruction, HRs from the lowest to the highest vitamin D status in tertiles were 1.00, 0.96 (0.87–1.05), and 0.89 (0.81–0.98), and 1.00, 0.96 (0.71–1.31), and 0.57 (0.40–0.80), respectively, in subjects with obstruction, in a multivariate model.

6 DISCUSSION

Our research group followed a national health examination cohort representative of Finnish adults for more than three decades. Obstruction predicted all-cause mortality by increasing GOLD stage and appeared detrimental especially when observed among subjects 30 to 49 years old. Additionally, obstruction predicted coronary mortality but not MI. Past TB and obstruction had an additive effect on all-cause mortality during follow-up. A low vitamin D status among subjects with obstruction in particular appears to predict premature death.

6.1 OBSTRUCTION AND MI AND CORONARY, CARDIOVASCULAR, AND ALL-CAUSE MORTALITY

6.1.1 ALL-CAUSE MORTALITY

In this study, our group found that obstruction predicted all-cause mortality according to the GOLD stage. This was consistent with previous studies [1,13,15-17,67,68].

In this study, age at baseline significantly modified the association between obstruction and all-cause mortality: it was strongest among men and women aged 30 to 49. A Danish study found a significant all-cause mortality trend among those with an obstruction at ≤ 45 years, and, similarly, a study from the USA reported that a lower FEV₁ at the age of 21 to 35 predicted all-cause mortality during follow-up times of 16–21 years and 33 years [15,132], respectively. Smoking is the main risk factor for COPD in Europe also among subjects aged 20 to 44 [133]. Therefore, in particular, smokers who develop obstruction at a younger age might have an increased mortality risk.

According to recent studies, the prevalence of smoking in Finland is decreasing among younger age groups as evidenced in one study among those under 18 years old and in another study among Finns aged 25 to 54. If this positive trend continues, the prevalence of obstruction may decrease in future. In the USA, a decrease in age-adjusted prevalence and mortality due to COPD among men has already been reported. However, in Finland, there was no change in the prevalence of COPD between the Mini-Finland Health Survey and the Health 2000 Survey, and the prevalence of smoking appear to increase among subjects aged 55 to 64. The increasing use of electronic cigarettes among subjects under 18 in Finland represents a concerning trend [3,134-136]?

6.1.2 CARDIOVASCULAR MORTALITY

In this study, we found that obstruction predicted cardiovascular mortality already for GOLD stage 1 while the risk was constant for GOLD stages 1–4 in age-, sex-, and smoking- and multivariate adjusted models. However, after excluding from the analysis those with a cardiovascular disease diagnosed at baseline, there was no association in these same models.

According to previous data, COPD and cardiovascular mortality both have association with decreasing lung function [13,18,65,71,76]. In a case–control study, COPD emerged as a risk factor for cardiovascular mortality [76], and a reduced FEV₁ predicted cardiovascular mortality even among never-smokers [65]. Subjects with mild to moderate COPD died more from cardiovascular diseases while those with more severe disease died from respiratory failure [13,19]. However, why in our material there was no significant increase in cardiovascular mortality among subjects without any cardiovascular disease at baseline remains unresolved.

6.1.3 CORONARY MORTALITY AND MI

In the current follow-up study, obstruction predicted coronary mortality but not MI except in the subgroup of younger women. According to earlier data, prevalent COPD and MI appear to predict all-cause mortality, while prevalent COPD predicts coronary mortality, also during long-term follow-up [15,18,22,79]. Yet, most studies on the association between COPD and coronary mortality were performed with shorter follow-up periods, among hospital patients, or with minor adjustments [9–11,15]. However, the multivariate adjusted results with the long-term follow-up in this study supported these previous findings.

Most studies found about COPD and MI were not directly comparable to the Mini-Finland Survey data since they were register-based, cross-sectional, included limited adjustments, or were performed for cohorts of hospital patients (Table 2). Yet, in the referenced studies, COPD predicted MI in two register-based and case-control studies [11,84–86], but not in one case-control study [83]. The cross-sectional studies reported both an association [22,74,81,85,87] or no association [75,82].

In the current follow-up study, obstruction predicted MI in the subgroup of women aged 30 to 49. In previous studies, the youngest subjects with COPD (aged < 45 or < 50 or 40–64) had a particularly increased risks of MI, fatal MI, coronary heart disease, and coronary mortality [15,74,84,85], while obstruction predicted coronary mortality more significantly among women under 45 years [15]. Additionally, impaired lung function at a younger age (16–35 or 21–35 years) predicts increased total, cardiovascular, heart, and cardiopulmonary mortality [132,137]. Furthermore, coronary heart disease appears different in men and women; in women, coronary heart disease concentrates among older populations, while younger women more often suffer fatal MI [138,139].

6.1.4 CARDIOVASCULAR DISEASES

Obstruction appears to have association differently with cardiovascular diseases compared to the disease's classic risk factors. These risk factors include for instance smoking, high LDL cholesterol, and hypertension, which have association with the risk for various cardiovascular diseases and deaths from them, including the endpoints analyzed in this study—that is, MI and coronary and cardiovascular death [140-145].

Previously, obstruction predicted cardiovascular diseases and cardiovascular and coronary mortality, although the association between obstruction and the risk of MI and stroke varied [8-11,15,18,22,79]. In our study, baseline cardiovascular disease appears significant for the association between obstruction and the cardiovascular endpoints analyzed. Obstruction predicted coronary death in a multivariate-adjusted model after those with baseline cardiovascular disease were excluded, but not cardiovascular mortality. The association between obstruction and MI was significant only in the subgroup analyses. No clear-cut inference could be made on the basis of this epidemiological study.

The associations between COPD and coronary and cardiovascular diseases appear complicated. Inflammatory reactions running behind these diseases might account for part of these conflicting results [1,20,22,23,82,146]. Additionally, the effect of hypercholesterolemia, hypertension, diabetes, and smoking as risk factors for cardiovascular diseases also appears partly induced by endothelium dysfunction caused by inflammatory reaction [146]. In addition, COPD and cardiovascular diseases share many risk factors such as smoking, ageing, and a low socioeconomic status; and both diseases and these associating factors predict chronic diseases and mortality complicating the further evaluation of these associations [1,8,9,12-14,147,148]. In general, it appears that obstruction may be involved in the prognosis rather than the etiology of cardiovascular diseases.

6.1.5 CONCLUSIONS: MI AND CORONARY, CARDIOVASCULAR, AND ALL-CAUSE MORTALITY

To summarize, obstruction predicts all-cause mortality; specifically, younger subjects with obstruction appear to have an increased all-cause mortality risk. Additionally, obstruction predicts coronary mortality, but not MI. However, younger women with obstruction might have an increased risk of MI.

6.2 PAST TB

This study revealed a cross-sectional baseline association between obstruction and past TB, and the association was stronger among those with a TB disease

history compared to those only with a TB indicative scar. These results corroborate previous findings [36,39-41,53,93].

In Danish and Norwegian studies, past TB, defined as a disease history or a TB indicative scar on a chest x-ray, predicted all-cause mortality in a long-term follow-up (materials were comparable with the Mini-Finland Health Survey data) [98,99]. In this study, a TB disease history did not predict all-cause mortality, but a TB indicative scar did. This apparently resulted from the low statistical power—that is, the Mini-Finland survey material included too few cases with a TB disease history for a significant result. A TB indicative scar predicted all-cause mortality possibly coincidentally; in addition, some observed scars were likely caused by diseases other than past TB, while the scars observed on subjects in the Mini-Finland Health Survey were not studied further. Moreover, we found that past TB and obstruction together predicted all-cause mortality through an additive pattern.

One particular strength in this study lies in that both experienced radiologists had previously participated in the x-ray screenings served for the entire Finnish population from the 1940s to 1990 [31]; furthermore, they both, independent of each other, analyzed all of the x-rays in the Mini-Finland Health Survey. Their reliability for diagnosing a TB indicative scar from a chest x-ray was evaluated and a moderate kappa was found, equating with an overestimation of TB diagnoses. Therefore, the diagnoses made by one or both radiologists were analyzed separately.

According to previous data, two experienced doctors could reliably diagnose TB on a chest x-ray if they had diagnostic agreement and the diagnostic reliability increased with a high TB incidence [149,150], as it was the case at the time of the Mini-Finland Health Survey [31-33].

To summarize, a TB disease history and a TB indicative scar on a chest x-ray have an association with obstruction, including among never-smokers. Past TB and obstruction predict all-cause mortality with an additive pattern.

6.3 ROLE OF VITAMIN D STATUS

Previous studies reported both an association and no association between a low vitamin D status and COPD. These conflicting results may be at least partly explained by the complex association between vitamin D metabolism, COPD, and multiple confounders [28,45,101]. At least in this study, the association between a low vitamin D status and obstruction was primarily attributed to confounding variables; a significant association in an age and sex adjusted model became non-significant in a multivariate model.

The complex association between a low vitamin D status and COPD complicates determining whether a low vitamin D status affects mortality in subjects with COPD [28,45,101]. In a literature review, only three previous studies analyzed the association between a low vitamin D status and all-cause mortality among subjects with COPD in a long-term follow-up study (10 to 18

years) [105,107,108]. Two studies showed no association [107,108], although in another study, a 25(OH)D concentration < 25 nmol/L had an association with all-cause mortality in subjects with a normal lung function [107]. The third study reported an association between a low vitamin D status and all-cause and cardiovascular mortality in subjects with COPD, yet the association was primarily attributed to cardiovascular risk factors. In that study, the limit for the lowest vitamin D status tertile was < 50.9 nmol/L [105], a level quite high compared to the Mini-Finland Health Survey data.

In this material, obstruction and a low vitamin D status predicted all-cause mortality independently of each other, although a low vitamin D status showed a stronger association with all-cause mortality in subjects with obstruction than in other subjects. Yet, the Mini-Finland Health Survey data have a low power, thus indicating the need for replication among a larger cohort before drawing any firm conclusions.

In brief, the baseline association between a low vitamin D status and obstruction was largely explained through confounding factors. We found that both a low vitamin D status and obstruction had an association with premature mortality, although the predictive strength of a low vitamin D status appears more pronounced in subjects with obstruction

6.4 REFERENCE VALUES AND DEFINITIONS OF OBSTRUCTION

No single definition for obstruction is in international scientific use; therefore, defining obstruction was problematic. International recommendations, definitions, and reference values for obstruction varied between 2010 and 2018 when this study was performed [1,54-56,58,63], and each study used the recommended definition that appeared most reasonable at that time or the definition recommended by referees.

Using different definitions for obstruction means that the results from studies I to IV were not directly comparable. For instance, the study I population included 463 subjects with $FEV_1/FVC < 0.7$ and 231 subjects < LLN, and respectively, 406 and 188 deaths in these groups. In comparison, the study II population consisted of 163 subjects with obstruction according to SAPALDIA < LLN and 210 according to GLI < LLN, and, respectively, 121 and 151 deaths in these groups. The same concern pervades the referenced studies which relied on various definitions and reference values for COPD (GOLD, LLN, register data with variable COPD definitions, or other; and SAPALDIA, GLI, or other reference values). In a previous study, the COPD prevalence was greater with a fixed cut-off limit compared to LLN, and the group falling in between these definitions appeared to have an increased risk for hospitalization and all-cause mortality [151].

The multi-ethnic GLI reference values are quite novel and validation of GLI in clinical use is currently taking place in various countries [58,63,152-154]. In Scandinavia, GLI appears valid in Norway, but not in Sweden or Finland. In the Finnish population, GLI and a fixed cut-off limit ($FEV_1/FVC < 0.7$) overestimate obstruction, while SAPALDIA has the best agreement with Kainu's reference values validated for clinical use in the Finnish population [56,57,61,152,154]. However, GLI appears to be a rational tool for international scientific use to produce internationally comparable data as well in the Finnish population.

Unfortunately, there were no follow-up data about subjects' COPD symptoms and exacerbations in this survey. Therefore, the GOLD's ABCD groups, recommended for clinical use from 2011, could not be used [1,55]. However, this doctoral study primarily focused on mortality. The GOLD stages 1–4 appear to predict all-cause mortality similarly [155,156] or even better compared to the ABCD groups [66,106], while the ABCD grouping appears to represent an improvement on phenotyping COPD and predicting exacerbations [155].

6.5 STRENGTHS

In studies I to IV, a representative Finnish adult sample population was followed continuously for 30 to 35 years through a national health examination survey. Featuring 90% participation rates at the baseline survey, specially trained and experienced professionals performed examinations using standardized methods [48,50,51]. The Mini-Finland Health Survey material consisted of a quite homogenous population with fewer confounders compared to the current Finnish population [32,33,48,110,157]. Additionally, the causes and dates of death were obtained from the death certificates as documented by the attending physicians [49,51]. The National Care Register for Health Care data is validated for MI patients [158].

When this data was collected in 1970s, TB incidence remained at high level in Finland, comparable with the current situation in developing countries [31,33], allowing our findings about past TB to remain relevant. The naturally low vitamin D status represents a particular strength of this material: when the material was collected, no vitamin D fortification was in use and working outside under the sun during the summertime was common [48,51]; vitamin D supplements complicate and confound analysis in more recently collected data [28,45,101,130].

6.6 LIMITATIONS

The study population included over 7000 subjects, yet, the low power emerged as the primary limitation; the limited number of subjects with obstruction

prevented analysis of factors such as the degree of obstruction, sex, age, and specific causes of death more precisely. Thus, the statistical power for subanalyses remained weak.

No bronchodilation was performed, and, therefore, some reversible obstruction might have been misclassified as chronic, although obstruction appeared to persist among those subjects who had obstruction during the Mini-Finland Health Survey baseline examination and were reanalyzed in the Health 2000 Survey. In the USA, COPD's prevalence varied from 20.9% (pre-bronchodilation values with a fixed cut-off limit for obstruction) to 10.2% (post-bronchodilation values with LLN) [159], yet pre- and post-bronchodilation lung functions appears to comparable predict all-cause mortality [160]. However, this deficiency was considered and in thesis was used a definition of obstruction when referring to our results and COPD when referring to others.

The Vitalograph spirometer used in the Mini-Finland Health Survey was at that time a commonly used device with an analog X-Y writer [50,126]. Yet, the accuracy of these spirometers differ from the modern digital flow-capacity spirometry devices used in recent decades [57,161]. Additionally, the first standard guidelines for spirometry were published in 1979, and, therefore, could not be applied in the Mini-Finland Health Survey, potentially affecting the quality of spirometry [127,161]. Yet, the spirometry results in the Mini-Finland Health Survey were reported according to the 1979 guidelines [50,127].

No information about lifetime pack-years smoked was collected. Thus, this parameter could not be analyzed. Smoking habits have changed in the Finnish population during the follow-up period—in the Mini-Finland Health Survey, 37.5% of men smoked (aged 30–74), 34.3% (aged 30–74) in the Health 2000 Survey and 25.2% (aged 25–64) in the 2012 follow-up survey. The comparable figures for women were 14.3%, 23.7%, and 17.9%, respectively. However, the prevalence for GOLD stages 2–4 remained unchanged between the Mini-Finland Health Survey and the Health 2000 Survey [3,134].

One specific weakness in the TB diagnostics is that the radiologists together formulated the diagnostic criteria for TB indicative scarring on a chest x-ray, but these criteria are no longer available. The scars were not classified more specifically. Another major change and limitation lies in the significantly improved vitamin D status in the Finnish population between 2000 and 2011 (vitamin D fortification policy from 2003) [34,100]. In addition, other baseline characteristics measured, such as weight and leisure physical activity, may have changed during follow-up affecting the results. These effects include changes in medical treatments for various diseases, particularly cardiovascular disease, and possible minor changes to causes of death and their documentation. These limitations are typically associated with retrospective health examination surveys.

7 CONCLUSIONS

In conclusion, bronchial obstruction predicts all-cause mortality based on the GOLD stage. Obstruction identified in individuals under 50 years old might be more detrimental than when diagnosed at an older age. In addition, obstruction strongly predicts coronary mortality, but not MI. Moreover, obstruction and past TB have an additive joint effect on all-cause mortality. Finally, a low vitamin D status may be more detrimental in subjects with obstruction than in others.

Thus far, little epidemiological research has focused on obstruction in relation to the size of the problem. Hence, further epidemiological studies should aim to add knowledge on its causes and consequences.

On the basis of this doctoral study, no clinical implication could be strictly proposed. In general, however, physicians should consider obstruction a significant risk factor for premature mortality.

We suggest the following topics for future studies:

- Why does obstruction predict coronary death, while the association between obstruction and MI remains less consistent?
- What are the pathophysiological mechanisms behind the association between obstruction and cardiovascular diseases?
- Is there any difference between COPD and obstruction in terms of the associations with cardiovascular risks and all-cause and cause-specific mortality?
- Could obstruction be an indicator for cardiovascular mortality risk?
- What role does obstruction measured in younger subjects play in their later morbidity?
- Do pulmonary infections other than TB serve as risk factors for obstruction?
- What unknown risk factors for COPD exist among never-smokers?
- What is the effect of a low vitamin D status on the prognosis for obstruction?

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